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PRESIDENT'S ADDRESS

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HUMAN feeling may be expressed in many ways: by the artist in form and in color, by the musician in composition and in interpretation, and by the writer in words so phrased as to bring to us his inner meaning.

My only medium is words, and I regret that I have not that facility in their use which would serve to convey to you all of the emotions which have stirred in me since you honored me by electing me your President.

There was first and uppermost the feeling of pride and joy that this honor should have come to me at your hands; but there has been also a constant undercurrent of doubt and dismay born of a realization of the lack in me of those qualities and attainments which have distinguished my predecessors in this Office. That you, in spite of these deficiencies, should still have deemed me worthy, places me forever in your debt for thus conferring upon me the greatest honor of my professional career.

In the year that has passed since our last meeting, death has taken a heavy toll; eight, Fellows, three of them former Presidents, have passed away. It is fitting that we pause for a brief space and recall them to memory.

NOTE.—This issue is, and a portion of the November number of the JOURNAL will be, devoted to the transactions of the Sixty-First Annual Meeting of the American Gynecological Society, Absecon, N. J., May 25 to 27, 1936. The papers are presented approximately in the order of their reading, together with the abstracted discussions. All of the contributions to the program are included with the exception of a paper by Dr. F. C. Irving, entitled "The Histologic Pathology of Placenta Accreta," which will appear in Surgery, Gynecology, and Obstetrics.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

William Blair Bell was elected to Honorary Fellowship in 1922 as a mark of appreciation, from his Colleagues here, of the work carried on by him in England. Honored in his own country as the first President of the British College of Obstetricians and Gynecologists, his death is a loss to the world at large.

Dougal Bissell was a very frequent contributor to our Transactions and will always be remembered for his investigations on the structures of the pelvic floor, and for the operative procedures which he devised and carried out for the repair of obstetric injuries.

Sir Kedarnath Das, elected an Honorary Fellow in 1923, was our guest in 1922, when he spoke to us on obstetric practice in India. He contributed much to scientific obstetrics and did an enormous service to India in raising the standards of teaching and practice in that vast country.

Francis Henry Davenport became a Fellow in 1889, was elected to the Honorary Fellowship in 1914, and died in the spring of this year at the age of eighty-five. He was for many years a teacher in the Harvard Medical School and practiced gynecology in Boston until 1914 when he retired from active work.

George Gellhorn had been a Fellow of the Society for thirty-two years and was President in 1932. He was a tireless worker, a man of original ideas, who was never afraid to put them to a practical test, a master of the English language, a philosophic thinker, and, at the same time, essentially a man of action. We all mourn his death and miss him.

In Barton Cooke Hirst, President in 1924, we have lost the doyen of our specialty in this country. He was a genial gentleman of the old school and was also a most up-to-date obstetrician and gynecologist, who has left his mark indelibly written on our records. We mourn for him as a scientist and as a dear friend.

Charles P. Noble was elected to the Society in 1891 and was Treasurer for some years. He was a prolific writer on obstetric and gynecologic subjects, and even after his retirement from active work he continued to interest himself in biologic problems.

C. Jeff Miller will always live in our memories as one who combined in a remarkable degree the attributes of the perfect gentleman, the genial companion, the cultured, widely read man, the practical investigator and teacher, and the wise counselor. His passing takes from us one whom we could ill spare. He occupied the President's Chair in 1929.

A wide latitude is allowed your President in a choice of a topic for his Address. During the ten years which have elapsed since I left my native Scotland to settle here and to become one of you (and for the heartiness of your welcome and for your unstinted kindness, I can never adequately express my appreciation), I have been increasingly interested in the exchange of ideas which has taken place between the two countries and, especially, in the influence that the Medical School of my Alma

Mater, the University of Edinburgh, had on the early development of medical education and practice here. I propose to recall to your memory some of the incidents and individuals in this connection.

In the days of the young American Colonies and at the time of the Declaration of Independence, the Medical School of Edinburgh was among the most renowned and the most progressive in Britain and in Europe. It was strong both on the surgical and on the medical side and was especially strong in anatomy. Its surgical and anatomical school began when, in the year 1505, the Town Council of Edinburgh granted a Charter to the Barber-Surgeons and recognized them as a distinct Craft. The present Royal College of Surgeons is the direct descendant of that Craft.

At the time of their incorporation, the Barber-Surgeons petitioned for and were granted the privilege of receiving from the City the body of one condemned man each year for dissection. This showed extraordinary enlightenment on the part of the Craft and of the City Fathers, for remember that at that time the Fathers of Anatomy, Vesalius and Fallopius, were not yet born, and that the Divines had not yet met at Salamanca "to determine if it were consistent with conscience to dissect the human body for the purposes of science." The Edinburgh Town Council not only granted the privilege, but they enjoined that the dissection be performed in public. Thereafter, each year the Craft appointed several of its members to carry out this dissection, each member taking up a different part of the body.

Very soon it was found that one body a year was not sufficient, and in the early Seventeenth Century the Barber-Surgeons again petitioned the Town Council and from it obtained permission to acquire "the bodies of fundlings who dye betwixt the tyme that they are weaned and their being put to schools or trades; also the dead bodies of such as are stiflet in the birth, which are exposed and have none to owne them; as also the dead bodies of such as are felo de se, and have none to owne them; likewayes the bodies of such as are put to death by sentence of the magistrat, and have none to owne them." The Council granted all this on condition that the surgeons before the year 1697 should have ready a properly equipped anatomic theater in which at least one public dissection each year be carried out. There is a full account in the records of the College of such a dissection performed in the year 1703. Eight members of the Craft took part in it, and the scene, as Miles says, must have been "not unlike that depicted by Rembrandt in his *Lesson on Anatomy.*"

Meantime the schools of anatomy in Europe were flourishing and notable discoveries were being made so that Scottish youths were attracted to the Continent for anatomic study. For their better instruction the Town Council, therefore, determined to appoint one man as Professor of Anatomy at a salary of £15 a year and to put on him the

responsibility of all teaching. Their reasons for this step were what are generally regarded (outside Scotland) as peculiarly Scotch, viz. "as an encouragement to young men to stay at home instead of travelling to foreign universities which is attended by expenses and other perils to youth."

The man appointed was Robert Eliot; the date of his appointment was 1705. He was the first Professor of Anatomy in Britain. This was the beginning of the Edinburgh School of Anatomy and was the foundation of the reputation which the Edinburgh Medical School held throughout the intervening years for anatomic teaching and research.

Eliot was succeeded by McGill, and then in 1720 Alexander Munro was appointed. He was succeeded by his son, Alexander Munro, secundus, and he, in turn, by his son, Alexander Munro, tertius, so that the professorship of anatomy remained in the hands of the Munro family for one hundred and twenty-six years. During these years students flocked to Edinburgh from all parts of the world. At one time there were as many as 800 students, many of them from the American Colonies, resident in the city for the study of anatomy alone.

The Colonists were also attracted to Edinburgh by the caliber of those who were teaching the practice of medicine. In the year 1726 a number of professors were appointed to the Edinburgh faculty. All of them had studied in Leyden under Boerhaave, the acknowledged Father of Clinical Medicine. They brought to Edinburgh his methods and tried to develop there a school like that of their master. Andrew St. Clair and John Rutherford were the pioneers, along with Robert Whytt at a later date.

In 1766 William Cullen was appointed Professor of Medicine and became the "Boerhaave" of Scotland. These were the men who attracted to Edinburgh young American colonists, who after obtaining their degrees returned to practice in their own land.

Benjamin Franklin was a great personal friend of Cullen and recommended many promising young men to him, among others William Shippen and Robert Morgan. Here is a letter from Franklin to Cullen written in 1760:

> I thank you for the civilities you were so good as to show my friend, Mr. Shippen, whom I took the liberty of recommending to your notice the last year. Give me leave to recommend one friend more to your advice and countenance. The bearer, Mr. Morgan, who purposes to reside some time in Edinburgh for the completion of his studies in physics, is a young gentleman of Philadelphia, whom I have long known and greatly esteem; and as I interest myself in what relates to him, I cannot but wish him the advantage of your conversation and instructions. I wish it also for the sake of my country, where he is to reside, and where I am persuaded he will be not a little useful.

Shippen graduated in Edinburgh in 1761, Morgan in 1762, and Benjamin Rush in 1768. Those three men, together with Adam Kuhn, also

an Edinburgh graduate, were the founders in Philadelphia of the first medical school in this country. The year was 1763.

While resident in Scotland, Rush became very friendly with a Presbyterian minister in Ayrshire, a descendant of John Knox, named Witherspoon. Witherspoon was invited to become the President of Princeton but refused. A second invitation was extended him and on the urgent pleading of Rush he accepted. Later both Witherspoon and Rush were signatories to the Declaration of Independence.

Samuel Bard was also a favorite pupil of Cullen. He graduated with the degree of M.D. in Edinburgh in 1765, and in 1769 became the first Professor of the Theory and Practice of Medicine in Kings College (now Columbia University), New York. To him New York owes the foundation of the City Hospital. Curiously enough, although Professor of Medicine, he wrote the first treatise on obstetrics in his country. David Hosach graduated in Edinburgh in 1794 and Latham Mitchell in 1784. "These three men (Bard, Mitchell, and Hosach) laid the foundation of the medical institutions of New York." (Osler.)

I should like to be able to say that Thomas Addis Emmet was a graduate of Edinburgh but I cannot do more than claim that his grandfather was one, of the year 1784. I should, likewise, like to claim Ephraim McDowell, the Father of Ovariotomy, but must be content with the fact that he did study anatomy and surgery under John Bell in Edinburgh during the years 1793 and 1794.

All of these great Americans retained a love for Scotland and Edinburgh as is shown by the letters they wrote to their former teachers, some of which I should like to quote to you but time forbids.

This fine exchange of courtesies was likely to be broken a century later when in 1870 Dr. Jacob Bigelow of Boston and Sir James Young Simpson of Edinburgh engaged in a wordy warfare over the priority of the discovery of general anesthesia and over the relative merits of ether and chloroform.

I suppose that most of us are to some extent hero worshipers, and I confess that Simpson is one of my heroes. This, in spite of the fact that in the writing of history in these latter days hero worship is no longer the vogue. The modern attitude is rather one of cold analysis with often an exaggerated emphasis on the faults and failings of the individual under discussion, bringing him down to our common level and ascribing to the times in which he lived and the attending circumstances the major credit for what he had achieved. Thus, Singer writing of Vesalius, the Father of Anatomy, says: ". . . he is in a sense, a lucky man in the position he holds in the scientific world. His great work was not the result of a long lifetime of experience . . . ; it was not wrought in the fierce heat of an intellectual furnace as was that of Pasteur or of Claude Bernard; it was not a task of subtle reasoning and skilled experimenting as was that of Harvey and of Hales. Vesalius was a very char-

acteristic product of his age. The womb of Time was in labor and it brought him forth. His intellectual father was the Galenic science that had gone before him. His mother was that fair creature the New Art, then in the very bloom of her youth. Until these two had come together there could be no Vesalius. When these two had come together there had to be a Vesalius."

Most epoch-making discoveries have been very simple in nature and almost self-obvious when expounded. The real kernel of many of them had been known years before the man or men arose who had the vision to perceive their importance and the energy and ability to work them out and to put them to practical use. These latter, rightly or wrongly, get the major credit for them.

In the history of the discovery of the principles of general anesthesia, the different anesthetic agents and their uses in surgery and obstetrics, these statements are amply illustrated. Around no other series of discoveries has such a warfare raged as that which followed the discovery of general anesthesia.

After Morton's successful demonstration of the anesthetic properties of ether in Boston in 1846, he was hailed as the hero and the pioneer. Horace Wells, who had induced anesthesia with nitrous oxide in 1844, and whose pupil Morton was, was for the time being forgotten, as was also Charles T. Jackson, Professor of Physics at Harvard, who had suggested the use of ether to Morton.

And Sir Humphry Davy was scarcely mentioned in spite of the fact that it was he who in the year 1800 had discovered the general anesthetic properties of nitrous oxide and had used it on himself for the relief of pain.

So heated did these discussions become that a Selected Committee of the Senate of the United States was appointed to settle the matter and their findings were published in a large volume of "Official Documents." Concurrently with and following this domestic discussion in the United States there arose the international dispute between Dr. Jacob Bigelow of Boston and Sir James Young Simpson of Edinburgh, Scotland, to which I have referred.

This controversy arose as the result of Bigelow's reading in an Edinburgh newspaper an account of the presentation of the Freedom of the City to Sir James Simpson. The Lord Provost in the course of his short speech of presentation said: "I will not dwell on what you have accomplished in medical science. I will only allude to the discovery—the greatest of all discoveries in modern times—of the application of chloroform in the assuagement of human suffering."

Bigelow upbraided Simpson because in his reply he made no mention of ether and of the discovery of its anesthetic properties by Morton in Boston. They were both accomplished letter writers and stated their

views in no uncertain way, and the whole correspondence makes most lively reading now. There was much misunderstanding on both sides but ultimately they agreed on the pertinent facts.

At the end of a very long letter to Bigelow, dated from Edinburgh, April, 1870, Simpson concludes the correspondence thus:

If we try to put into a summarized form the data which we have been discussing regarding the introduction of anesthesia in America and this country, it appears to me that we might correctly state the whole matter as follows:

1. That on the eleventh of December, 1844, Dr. Wells had, at Hartford, by his own desire and suggestion, one of his upper molar teeth extracted without any pain, in consequence of his having deeply breathed nitrous oxide gas for the purpose, as suggested nearly half-a-century before by Sir Humphry Davy.

2. That after having with others proved, in a limited series of cases, the anesthetic powers of nitrous oxide gas, Dr. Wells proceeded to Boston to lay his discovery before the Medical School and Hospital there, but was unsuccessful in the single attempt which he made, in consequence of the gas-bag being removed too soon, and that he was hooted away by his audience, as if the whole matter were an imposition, and was totally discouraged.

3. That Dr. Wells's former pupil and partner, Dr. Morton of Boston, was present with Dr. Wells when he made his experiments there.

4. That on the thirtieth of September, 1846, Dr. Morton extracted a tooth without any pain, while the patient was breathing sulphuric ether, this fact and discovery of itself making a NEW ERA in anesthetics and in surgery.

5. That within a few weeks the vapour of sulphuric ether was tried in a number of instances of surgical operations in Boston—Dr. Morton being generally the administrator; and ether vapour was established as a successful anesthetic in dentistry and surgery.

6. That in January, and the subsequent spring months, 1847, the application of sulphuric ether as an anesthetic in midwifery was introduced, described in our medical journals, and fully established in Edinburgh, before any case with it was tried in Boston or America.

7. That on the fifteenth of November, 1847, the anesthetic effects of chloroform were discovered in Edinburgh, and that it swiftly superseded in Scotland and elsewhere the use of sulphuric ether, and extended rapidly and greatly the practice of anesthesia in surgery, midwifery, etc.

The letter continues:

I am very sorry to have taken up so much of your time and my time with such a petty discussion as the present. It has extended to too great a length; but I am a sad invalid just now, and quite unable to write with the force and brevity required. With many of our profession in America I have the honour of being personally acquainted, and regard their friendship so very highly that I shall not regret this attempt—my last perhaps—at professional writing as altogether useless on my part, if it tend to fix my name and memory duly in their love and esteem.

Yours very truly,

J. Y. SIMPSON.

The news of Simpson's death reached Boston by cable before his letter arrived and the Gynecological Society of Boston held a Memorial Meeting in honor of their "late beloved associate" who was, they said, "one of nature's noblemen."

Thus, the ultimate result was that Simpson freely acknowledged, as he had always done, that Morton was the first man to produce general anesthesia to the surgical degree by the administration of ether, and Bigelow acknowledged that Simpson was the first man to use ether as an anesthetic in obstetrics, and that he discovered the anesthetic properties of chloroform.

Neither of these contributions of Simpson came to fruition in any haphazard way. Both were the result of deep thought and of hard experimental work. Both were defended against the attacks of all sorts and conditions of people with a dialectic skill and a dogged persistence which mark Simpson as a real man of genius, if genius consists of "an infinite capacity for taking pains."

Let us first try to picture what sort of man he was. Born of poor parents (his father was a baker) in the village of Bathgate in the year 1811, he was the youngest of seven children. His early education was begun in the village school at the age of four in the year of the Battle of Waterloo, and completed at the age of fourteen when he entered the Faculty of Arts of the University of Edinburgh.

As was common with poor Scots' families of these times and later, all of the family resources were called upon and all sorts of economies were effected in order to provide funds to send the promising son to college. And James Simpson gave great promise, for not only was he head of his school at the age of fourteen but had already, in the study of the flora and geology of the countryside, begun to show that power of observation and that faculty for the acquisition of facts which characterized all his later scientific work.

He never completed his Arts course, for after two years he was attracted to medicine. He had attended all the necessary classes and passed his final examination for the medical degree while still in his teens and had to wait for two years before he could be licensed to practice. This time was occupied in attending again the class of midwifery, in acting as assistant to the professor of pathology, in assisting the doctor in his native village, and in travel to London and to the Continent of Europe. The funds for the latter were again provided by his devoted family.

He began his professional career in Edinburgh as a general practitioner but early devoted his attention to midwifery, obtaining an appointment to the Lying-In Hospital and starting a lecture course for students in obstetrics.

Meantime, he had begun to write and to publish papers on pathology which received wide attention, not only in Scotland but also in Europe.

When he was twenty-eight years old, the professorship of midwifery in the University fell vacant and Simpson became a candidate for the Chair. The power of appointment was in the hands of the Town Council of the City and the contest between Simpson and his chief rival, Ken-

nedy of Dublin, was very keen. Simpson put all of his enormous energy into the fight, even going so far as to acquire a wife at short notice, when he learned that his state of bachelorhood was being used as an argument against him. He spent £500, a large sum in those days, on the preparation and distribution of his testimonials, which made a volume of 150 octavo pages. "His aim was to make known his scientific attainments, powers as a teacher, and personal qualifications, which he felt, if duly realized, would outweigh the disadvantages of his youth and comparative inexperience."

After a spirited contest he was elected by a majority of one and with that matter settled immediately directed his prodigious energy and enthusiasm to his chosen subject.

Not content with the narrower field of obstetrics he did pioneer work in the field of diseases of women, and must be regarded as one of the founders of modern gynecology. Had he done nothing at all for anesthesia his name would have lived for his contributions to this subject.

Simpson was an omnivorous reader, not only of medical but also of general and, especially, of antiquarian literature, and (as we shall see presently) was a theologian of no mean order who knew his Bible from beginning to end. A man of fine sensibilities, the suffering of his parturient patients always distressed him. He tried all sorts of drugs and even resorted to experiments in hypnotism in an effort to relieve them. Among all his other interests, this one was ever present in his mind.

When, therefore, news reached Edinburgh from across the Atlantic that Morton in Boston on Oct. 16, 1846, had successfully induced anesthesia by the inhalation of ether and that Liston had subsequently used it in London, Simpson was thrilled and immediately thought of its possibilities in obstetrics.

The problem that faced him was a harder one than that which confronted the surgeon. In those days the surgeon did his work quickly, so that the patient did not require to be long under the influence of the anesthetic.

The problem presented to Simpson was twofold. Could the anesthesia be continued sufficiently long to give appreciable relief? And would the anesthetic interfere with uterine contraction?

He chose for the first trial a case of contracted pelvis, calling for the operation of version. He waited for this case because, from the nature of the operation, any interference with uterine contraction by the anesthetic would be of little moment. On Jan. 19, 1847, the operation was successfully and painlessly performed under ether anesthesia, and Simpson was able to satisfy himself that uterine contraction went on normally. He, therefore, proceeded to employ it in normal cases, an account of which he read before the Edinburgh Obstetrical Society

on Feb. 10, 1847. The practice was soon taken up in Scotland, in England, in Germany, and, a few months later, in America.

Not being altogether satisfied with ether, because of the large quantities required in prolonged cases, and because of the bronchial irritation to which it often gave rise, he had sent to him by different chemists various volatile substances which might be inhaled. With these he experimented on himself and on his friends.

Among these substances was a small quantity of chloroform, which he had procured from Messrs. Duncan and Flockhart. Mr. Waldie, a Scotsman in business as a chemist in Liverpool, had suggested to him that this was probably the anesthetic substance in the chloric ether which Bigelow in Boston and Liston and Jacob Bell in London, had used successfully.

Here is the story of the discovery, as it is graphically told by Professor Miller, a near neighbor of Sir James Simpson in Queen Street, Edinburgh, and quoted by his nephew and successor in the Chair, the late Sir. A. R. Simpson:

Most of these experiments were performed after the long day's toil was over, at late night or early morn, and when the greater part of mankind were soundly anesthetized in the arms of common sleep. Late one evening, it was Nov. 4, 1847, on returning home after a weary day's labor, Dr. Simpson with his two friends and assistants, Drs. Thomas Keith and J. Mathews Duncan, sat down to their somewhat hazardous work in Dr. Simpson's dining room. Having inhaled several substances, but without much effect, it occurred to Dr. Simpson to try a ponderous material, which had been formerly set aside on a lumber table, and which, on account of its great weight, he had hitherto regarded as of no likelihood whatever. That happened to be a small bottle of chloroform. It was searched for, and recovered from beneath a heap of waste paper. And, with each tumbler newly charged, the inhalers resumed their vocation. Immediately an unwonted hilarity seized the party; they became bright-eyed, very happy, and very loquacious, expatiating on the delicious aroma of the new fluid. The conversation was of unusual intelligence, and quite charmed the listeners, some ladies of the family and a naval officer, brother-in-law of Dr. Simpson. But suddenly there was a talk of sounds being heard like those of a cotton mill, louder and louder; a moment more, then all was quiet, and then, a crash. On awakening, Dr. Simpson's first perception was mental: "This is far stronger and better than ether," he said to himself. His second was to note that he was prostrate on the floor, and that among the friends about him there was both confusion and alarm. Hearing a noise, he turned round and saw Dr. Duncan beneath a chair, his jaw dropped, his eyes staring, his head bent half under him; quite unconscious, and snoring in a most determined and alarming manner. More noise still, and much motion. And then his eyes overtook Dr. Keith's feet and legs making valorous efforts to overturn the supper table, or more probably to annihilate everything that was on it; I say, more probably, for frequent repetitions of inhalation have confirmed, in the case of my esteemed friend, a character for maniacal and unrestrainable destructiveness, always under chloroform, in the transition stage.

By and by, Dr. Simpson having regained his seat, Dr. Duncan having finished his uncomfortable and unrefreshing slumber, and Dr. Keith having come to an arrangement with the table and its contents, the sederunt was resumed. Each expressed himself delighted with the new agent, and its inhalation was repeated many times that night, one of the ladies gallantly taking her place and turn at the table, until

the supply of chloroform was fairly exhausted. It is of interest to note that Keith was elected to the honorary fellowship of this society in the year of its foundation and Mathews Duncan two years later.

There can now be no question but that to Simpson belongs the sole credit of being the first to suggest and to use general inhalation anesthesia in labor, and that he was the first to demonstrate the anesthetic property of chloroform. While time has not confirmed Simpson's assertion that chloroform was a better and safer anesthetic than ether, some of us still regard it as having a very definite place in obstetrics.

But with these discoveries, Simpson's task had only just begun, for immediately there arose a clamor from the medical profession and from the Church against the use of anesthetics in labor. It was fortunate that Simpson was a man of such strong convictions, such iron will, and so skilled in debate as to beat down that opposition.

One of his most bitter opponents was Professor Meigs of Philadelphia. Which of us today could write as Simpson did to Meigs in 1848? His letter begins as follows:

Edinburgh, August, 1848

My dear Sir:

A few days ago, I saw your excellent epistle to me on the use of anesthesia in midwifery, extracted, in an abridged form, from the Philadelphia Medical Examiner of March last, into the London Medical Gazette and Lancet. It reminded me, that amid other avocations and work, I had hitherto indolently omitted to answer the objections contained in your able and kind letter. And I feel that I am the more to blame for this neglect, on one account, namely, that as in your own country, so also in ours, there are few or no living obstetricians, whose opinions and names carry, and deservedly carry, more weight with them than yours. Be so good, then, as to bear with me now for a few minutes, while I endeavor to state in what respects I am inclined to demur to your arguments against anesthetic midwifery.

On reperusing, as I have just done, your esteemed letter, it appears to me that in it you ground your opposition to the adoption of anesthesia in midwifery upon four or five different arguments, although you do not specialize them. I shall notice each of these arguments separately. You have not placed them in any particular order. I shall begin first with the one which you placed last.

So polite and yet with such veiled sarcasm. He then proceeds to demolish each of Meigs' arguments, the whole letter extending to twenty closely printed pages. Allow me to quote one small section of his reply to Meigs' objection to anesthesia in natural labor, on the ground that the pain of natural labor is a "physiological pain":

You are well aware that the act of parturition has been often familiarly compared, as the late Professor Hamilton expressed it, "to the toils of a journey," and like it divided into stages. "The sufferings of the mothers," says he, "have been in most languages compared to those of travellers." Now let us for a moment continue this natural simile between the function of parturition and the function of progression. You maintain that "labour is the culminating point of the female somatic forces." One of the most illustrious Presidents of your great American Republic, Thomas Jefferson, makes in his memoirs a remark of precisely the same

import regarding walking or progression. He describes the act of walking, but not exactly in the same words, as a kind of "culminating point of the human somatic forces."

"Walking," says the American President, "is the best possible exercise; habituate yourself to walk very far." "The Europeans," he continues, "value themselves on having subdued the horse to the uses of man; but I doubt whether we have not lost more than we have gained by the use of this animal. No one has occasioned so much (as the horse) the degeneracy of the human body. Our Indians go on foot nearly as far in a day, for a long day, as an enfeebled white does on his horse; and he (the Indian) will tire the best horses."

Few, or none, perhaps, will question the abstract truth of Jefferson's observations on this point. But, because walking or progression is a "physiological" function, and the practice of it is reputed salutary, would this be, with you, a proper and sufficient reason for never setting aside or superseding in any way this "physiological" state, in the same way as you insist, on the same grounds, that the physiological pain of labour should not be set aside or superseded. Because progression is a natural condition, would this be any adequate reason for your medical advisers adopting your own arguments against anesthesia in midwifery, and insisting upon this, that, the next time you travelled from your own city of Philadelphia to the cities of Baltimore or New York, you should walk the distance on foot instead of travelling it by railway or other conveyance? What opinion would you form of the judgment of any medical adviser to whom you entrusted your own health, if, on going next time to the New York or Baltimore railway station, he should gravely and solemnly repeat to you, as his patient, what you tell your midwifery patients, and, in your own language, advise you to try to accomplish the intended journey on foot, as (to quote your own words) "a desirable, salutary, and conservative manifestation of life-force"?

Painstakingly, always in the most courteous but at the same time in the most forceful language, Simpson wrote many such letters in reply to his medical critics. These will be found reproduced in extenso in the volume of collected papers entitled *Works of J. Y. Simpson* edited by his son in a volume and published by D. Appleton & Co., New York, in 1872. I should like to quote much more extensively from them but time forbids. Let me recommend them to you for leisurely perusal.

The clerical objectors were similarly paid back in their own coin, for Simpson being a good Scots Presbyterian knew his Bible thoroughly. Here is an extract from one of his letters controverting the views of the Church on the sinfulness of abolishing the pains of labor and so nullifying God's curse on woman "in sorrow thou shalt bring forth children":

If, on religious grounds, your obstetric friends object to relieving entirely a woman of her worst pains, now that they have the means of doing so, they must, on the very same grounds, refuse to relieve her imperfectly and partially of these or any other pains and sorrows connected with parturition; they must, or at least ought to, abstain, in fact, from all obstetric practices whatsoever; they should, in short, give up their present profession as a profession of sin, and "in the sweat of their face" eat bread. I can see no other possible alternative for them, provided, that is to say, they choose to reduce actually their theory into practice. If on the other hand, they think it not sinful to relieve their female patients, to a small amount, from the alleged sufferings entailed upon them by the first curse, then surely it is not sinful in them to relieve their patients from their sufferings to a far

greater amount, now that they have the power of doing so, nay, is it not sinful in them obstinately to withhold that relief? For, "to him that knoweth to do good, and doeth it not, to him it is sin."

And if any of your female patients hold the same groundless doctrine, a doctrine far more in accordance with the blindness and fatalism of Mahommedanism, than with the spirit and genius of Christianity, if they hold that it is improper, for scriptural reasons, to abrogate the pains and sufferings of childbirth, then such mothers cannot conscientiously content themselves with rejecting merely the use of chloroform in medical assistance in their hour of travail; they must give up, indeed, all assistance whatever. If the supposed pains and perils of the primeval curse are to be submitted to, on the ground that they are divinely appointed and unavoidable ordeals, then they must be submitted to in all their unmitigated power and plenitude; no doctor must sinfully dare to stay the ebbing stream of life, if a fatal flooding suddenly supervene during labour; no nurse must venture, as heretofore, to relieve and mitigate the agonies of the shrieking mother by counter-pressure to her back, etc., "for whosoever shall keep the whole law, and yet offend in one point, he (she) is guilty of all."

It seems very strange that such arguments should have been necessary in the year 1848, not one hundred years ago. That they were necessary is shown by the number and the length of the letters which Simpson wrote. He must have covered reams of paper and have expended on them an incalculable amount of energy.

In this country he had a worthy supporter in Walter Channing of Boston. Thoms (Walter Channing and Etherization in Childbirth, Am. J. Obst. & Gynec. **20**: 244) has recently written a short memoir of him pointing out how Channing played the same part in answering medical, lay, and clerical criticism here as did Simpson in Scotland.

Both of them had the satisfaction before they died of knowing that their efforts had not been in vain.

It is always interesting to try to picture the physical make-up of men who have had their names written upon the Book of Fame. Numerous photographs and portraits of Sir James Young Simpson exist. He was described, somewhat fulsomely, by a contemporary as follows:

In stature the Professor is somewhat under the middle size. The roundness of his whole form and the absence of Scotch "processes of bone" would authorise the inference of English extraction. His ambrosial locks, dark and almost imperceptibly shaded with red, fall upon his shoulders. No feature in the Professor's countenance is overgrown. The forehead is broad and projecting rather than lofty. There is much firmness about the mouth and the lips. The eye is brilliant, and looks out from the eyebrows with an energy and penetration betraying great mental power. With the fiercer radiation of its eagle fires is blended the soft glow of a warm heart, which gives it a decided intellectual and moral expression. There is a fascination in his air, manners, and conversation, an irresistible moral gravitation which elicits and wins the admiration, love, and confidence of all who come within the magic circle of its influence.

A medical colleague wrote in 1848:

Decidedly the most wonderful man of the age in which he lives is Simpson of Edinburgh. Nothing baffles his intellect, nothing escapes his penetrating glance, he sticks at nothing, he bungles nothing. From all parts, not of Britain only, but of Europe, do ladies rush to see, consult, and fee the little man.

Another described him as possessing "the head of Jove, the body of Bacchus."

And so I confess that I am sentimental enough to be a hero worshiper and to feel that we can derive inspiration and courage from a reperusal of the lives of great men. Such study teaches us that dry-as-dust knowledge is not everything. The great physician, the great surgeon must of necessity be more than a scientist or a technician. He must have that something which we call personality, and he must have interests outside those of his calling. So it behooves us to take care that our present hidebound regulations for the admission to the study of medicine, and our rigid scientific curricula do not exclude and do not dampen the enthusiasm of some who, if given the opportunity, might develop into great clinicians.

ANEMIA IN PREGNANCY

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INNUMERABLE reports have been published about the etiology and treatment of anemia in pregnancy. Some investigators have reported improvement but none, so far as we know, have reported failures with various types of therapy. The frequency of anemia in pregnancy in a large series of patients should be determined and notation made of what happens if these same patients are not treated and what the results are if they are treated.

Various types of anemia occur during pregnancy. The first and most common is the so-called "physiologic anemia" of pregnancy. This is demonstrated by the curves shown in Fig. 1, which represent hemoglobin and cell volume determinations obtained during pregnancy by various investigators. The different figures given for hemoglobin have been recalculated to a standard of 100 per cent, containing 14.3 gm. per 100 c.c. Kühnel, in a serial study of the *same* 15 patients during pregnancy and the puerperium with carefully controlled methods, concluded that there is a gradual drop in hemoglobin, cell volume and erythrocyte count until the sixteenth to twenty-second week. This low level is maintained until about the thirtieth to thirty-second week when these substances begin to increase but reach a figure at thirty-four to thirty-six weeks which is lower than the initial figure. The hemoglobin concentration is not normal until weeks and occasionally months after delivery. Curve 2 in both figures is taken from his work.

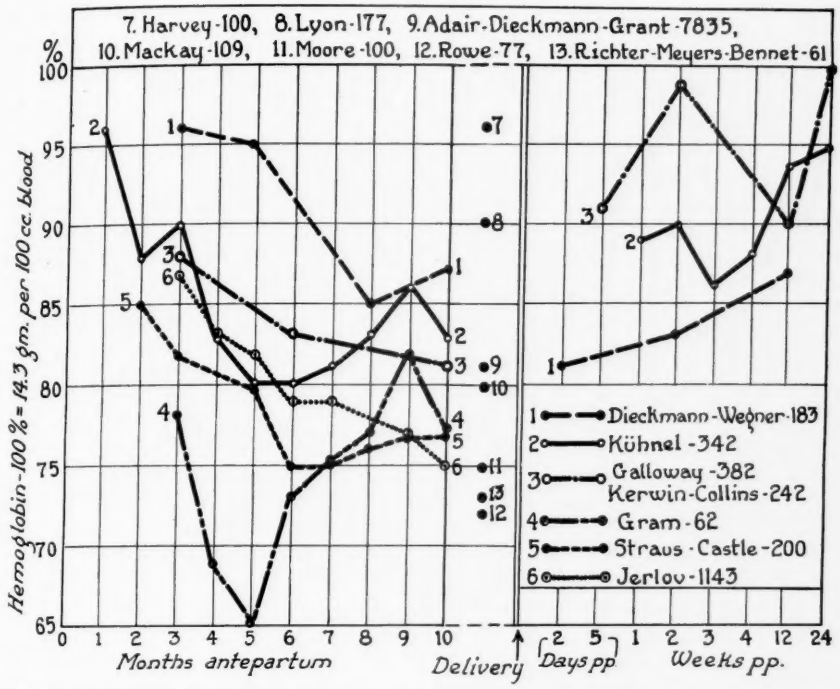


Fig. 1-*A*.—Graph illustrating the hemoglobin curves in pregnancy as reported by various investigators.

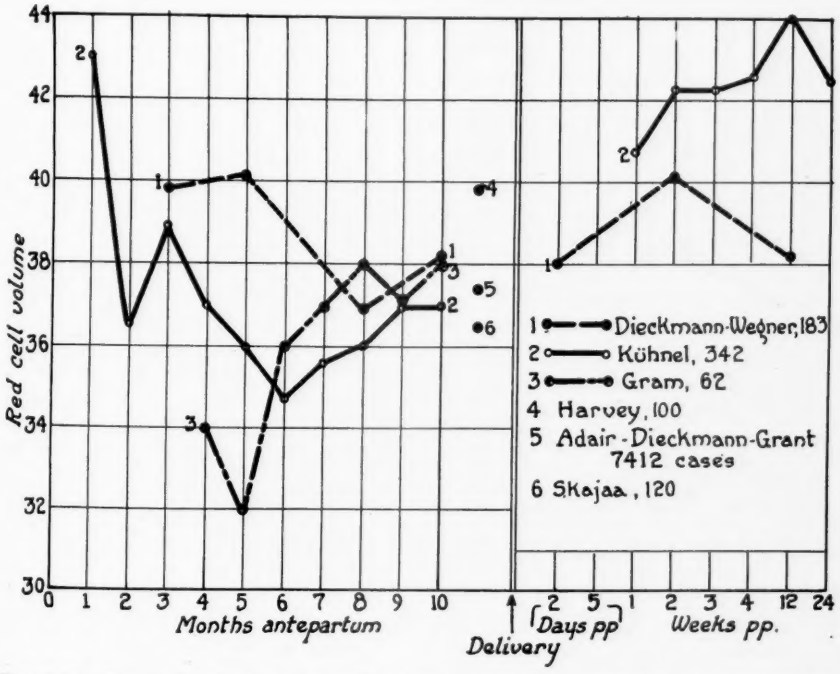


Fig. 1-*B*.—Graph illustrating the cell volume curves in pregnancy as reported by various investigators.

Dieckmann and Wegner (curve 1 in Fig. 1), like Kühnel, followed the *same* patients during pregnancy and the puerperium. Determinations of blood and plasma volumes and exact determinations of hemoglobin, cell volume and cell counts were made at periodic intervals. They concluded that at term the blood volume shows an average increase of 23 per cent, the plasma of 25 per cent, and the total erythrocyte mass of 20 per cent. This discrepancy of 5 per cent accounts for the decrease in hemoglobin concentration, cell volume, and erythrocyte count seen in normal pregnancy. This phenomenon is termed the "physiologic anemia."

They further found that there is an average decrease in the hemoglobin concentration in normal pregnancy amounting to 15 per cent at twenty-five to thirty-five weeks. From then on until term, the hemoglobin increases and may reach a normal level. They reported that the total amount of hemoglobin showed an average increase at term of 13 per cent, but this increase in hemoglobin is less than the increase in blood volume. They stated that many of the previously reported figures for hemoglobin, cell volume and erythrocyte counts in pregnancy are in many instances at variance with each other and the results are inconclusive because, with but few exceptions, the determinations were made with methods and apparatus which were not standardized and the *same* women were not followed throughout pregnancy. Wintrobe, Haden, and Osgood and Haskin in a careful study of nonpregnant women have shown that the lower limit of normal for the hemoglobin concentration is 12 gm. Dieckmann and Wegner concluded from their work that in pregnancy the lower limit of normal is 10 gm. per 100 c.c. of blood. They also showed, and apparently for the first time, that during pregnancy there are marked individual variations in the same women of all of the indexes, especially of the color indexes, but the average for each remains close to one. In the study of the individual cell, they found that the corpuscular volume is increased slightly between the twenty-sixth and thirty-fifth week when the physiologic anemia is most marked. The corpuscular hemoglobin is increased slightly both in amount and in percentage during the greater part of pregnancy, but it is normal at term and during the puerperium. The hemoglobin and the volume coefficients are increased during the greater part of pregnancy, but they are essentially normal at term and during the puerperium. They stated that the amount of hemoglobin per kilogram of body weight increased slightly during pregnancy.

A second type of anemia in pregnancy occurs in women who have a subnormal hemoglobin in early pregnancy and when the "physiologic anemia" occurs, the drop in hemoglobin is so great that symptoms and signs of anemia occur, which may clear up after delivery or may persist. This is usually a microcytic type of anemia with the corpuscular volume ranging between 70 to 80 cu. μ. This group forms the vast portion of anemia in pregnancy, and the patients as a rule have no symptoms or signs of the condition.

Strauss and Castle examined the gastric juice, both fasting and after a test meal, and determined the hemoglobin concentration in a number of pregnant women. They concluded that 18 out of 24 or 75 per cent of their patients showed an acid secretion below the normal range during more than one-half of the period of pregnancy. They also concluded that the anemia of pregnancy (not the physiologic type which they thought was probably due to a hydremia) which occurs during the last trimester of pregnancy, is due to the demands of the fetus for blood-forming substances, and "is found only in those patients who have had for a considerable time a defective diet or dietary deficiencies conditioned by gastric anacidity or related gastrointestinal disturbances." They stated that the

hypochromic anemia of pregnancy could be relieved, *without exception during pregnancy,* by the daily administration of 6.0 gm. of iron ammonium citrate. This conclusion is based on studies made on 30 patients with the hypochromic microcytic anemia and 6 with the macrocytic anemia.

A third type is rare and is characterized by a larger cell, ranging from 90 to 130 cu. μ. These patients usually have symptoms and signs of anemia and at times seem to have a toxemia of pregnancy as indicated by edema and albuminuria. The blood smears show all the characteristics of a pernicious anemia and occasionally the differential diagnosis is difficult. As a rule, there are no neurologic findings and the characteristic increase in reticulocytes does not occur after administration of liver. Such patients were formerly designated as having pernicious anemia of pregnancy. The mortality rate was quite high, and it was probably such patients who were described by Channing and Osler.

An anemia occurring in pregnancy with a maternal mortality of 40 per cent and a fetal one of 63 per cent has been repeatedly described in Indian medical journals. This anemia has been reported in both men and women, but its greatest incidence is in pregnancy. Recovery does not take place until after delivery, when it may occur spontaneously. The anemia is due to a deficient diet as Wills has demonstrated that the feeding of marmite (brewer's yeast) will cure the disease. Furthermore, she has been able to produce a similar anemia in monkeys by eliminating protein and yeast from their diet and to cure it by feeding them these substances.

An editorial was published in the *Indian Medical Gazette* for 1932 which gives not only the history of anemia of pregnancy but also summarizes all of the Indian reports. The "Indian" anemia occurs in 2.93 per cent of their hospital deliveries. The onset is usually abrupt and occurs between the fifth and seventh month of pregnancy. Balfour found that one-half of the patients had an initial fever and 83 per cent had fever some time during the disease. Most of the cases occur between October and March. Seventy-five per cent of the women are between fifteen and twenty-nine years of age. A third of the cases occur in the first pregnancy and another third occur in the second and third pregnancies. The patient's skin is pale, flabby and looks edematous. Tachycardia, dyspnea, vomiting, diarrhea, weakness, sore mouth, albuminuria, edema, hypotension, palpable liver and spleen are the usual symptoms and signs. The gastric juice contains free HCl and is normal in all respects. Bacteria are quite commonly found in the urine. The average erythrocyte count is 1,210,000, the hemoglobin is 33 per cent and the color index is 1.4. Anisocytosis, poikilocytosis and some polychromatophilia, normoblasts and megaloblasts are noted in the blood smears. Postmortem examination reveals very pale organs containing free iron.

Labor is an added risk. There is exceptionally little blood loss during the third stage, but labor is apparently too much of a strain on the heart because 21 per cent of the patients die during delivery or within the first week postpartum. The babies are small, usually weighing less than 5 pounds. Their hemoglobin is normal at birth.

A therapeutic abortion should be performed if the patient is seen in the first three months. Since the disease as a rule does not occur or is not noticed until later in pregnancy, the treatment is entirely medical. A proper diet with the

addition of liver and marmite (yeast) should be instituted. Twenty c.c. of blood injected intramuscularly once or twice a week appears to be of value. Blood transfusion apparently starts labor and is therefore contraindicated. While the disease does not seem to recur, future pregnancies should be prevented.

METHOD

Blood was taken from an arm vein without stasis and heparin was used as an anticoagulant. The cell volume was determined by centrifuging the blood in Wintrobe hematocrit tubes for a period of one hour at 3,600 r.p.m. The amounts of hemoglobin were determined with a Newcomer pipette and colorimeter, using a glass color plate and blue filter. The plate was standardized by the oxygen capacity method and found to need no correction. Duplicate hemoglobin specimens were usually analyzed in the chemical laboratory every two weeks with a carbon monoxide method. Erythrocyte counts were made with the usual technic but the chambers and pipettes were standardized against a chamber and pipette certified by the Bureau of Standards. The cell volume method has a maximum error of 2 per cent. The Newcomer method, with an exact technic, has an error of 5 per cent, but with the usual technic entailed in a clinic laboratory in which as many as 75 to 125 patients daily were examined by two technicians, the possible error was 8.7 per cent. Likewise, the possible error in the red cell count in the clinic laboratory amounted to 13.7 per cent, while the same technician with careful technic which was time consuming could reduce the error to 2 per cent. The error in the cell volume was not affected by the number of patients examined and is the most foolproof of the three determinations. All determinations have been made by three technicians and no change was made in technic at any time.

Various observers have shown that the hemoglobin, cell volume and cell count, although constant for the individual, do fluctuate during the period of a day. The hemoglobin may fluctuate as much as 15 per cent (2.07 gm.) and the cell volume and erythrocyte each 3 and 17 per cent, respectively. Thus in attempting to determine the value of any medication, one has to take into account the inherent error of the determination, the normal curve of hemoglobin in pregnancy as well as the hourly fluctuations of hemoglobin.

Our statistical data are summarized in Table I. Series I comprises all pregnant patients admitted during the period from March, 1932, to March, 1934; Series II, the period from March, 1934, to November, 1935. The total series is composed of I and II. The private group consisted of all patients who were delivered by members of the department staff during 1934. The gynecologic group was composed of all nonpregnant patients, excluding only those who had been pregnant within three months.

Series I and II were studied separately because they check against each other, since there was no change in technic or personnel during the four-year period. It is of interest that for the total series the average hemoglobin is 11.56 as com-

pared with that of Dieckmann and Wegner of 12.5; that the mean cell volume is 37.31 as compared with that of 36.9, and the mean erythrocyte count is 3.77 as compared with that of 4.20.

In Fig. 2 *A*, *B*, and *C* are shown the frequency distribution of the hemoglobin, cell volume, and red cell count. It is obvious that the maximum number of cases fall in the groups with 10, 11, and 12 gm. of hemoglobin and in the 35 to 44 volume per cent groups for the cell volume and the 3.40 to 4.19 groups for the red cell count. These average frequencies for the various substances are decidedly less than those reported for the nonpregnant woman.

Fig. 3 is a frequency graph in which the hemoglobins for various groups of patients are compared. It is obvious that the greater number of gynecologic patients, even with obvious anemias included, fall in the 11, 12, 13, and 14 gm. groups. In this group 1.5 per cent were under 8.0, 3 per cent were under 9.0,

TABLE I. SUMMARY OF THE STATISTICAL DATA

	ALL PREGNANT PATIENTS			PRIVATE OBSTETRIC PATIENTS 1934	ALL GYN. PATIENTS 20 MO.
	SERIES I 24 MO.	SERIES II 20 MO.	TOTAL SERIES 44 MO.		
Hemoglobin—Gm. Per 100 c.c. of Blood					
Number of patients	4,342	3,493	7,835	170	2,399
Mean ±	11.42	11.76	11.56	11.79	12.76
Probable error	>0.001	>0.001	>0.001	0.065	>0.001
Standard deviation	1.4	1.4	1.4	1.26	1.68
Range			4.0-16.9	8.0-15.9	4.0-16.9
Cell Volume—Volumes Per Cent					
Number of patients	4,168	3,528	7,696	135	1,227
Mean ±	37.4	37.2	37.31	38.46	40.76
Probable error	>0.01	>0.01	>0.01	0.218	>0.01
Standard deviation	4.2	4.2	4.2	3.76	5.07
Range			15-54	25-49	15-54
Erythrocytes—Millions					
Number of patients			4,345	168	
Mean ±			3.77	3.801	
Probable error			0.001	0.0195	
Standard deviation			0.405	0.375	
Range			1.60-5.00	2.80-5.00	

5.8 per cent were under 10, 11.7 were under 11, and only 25.8 were under 12. Comparable figures were obtained for cell volume and cell count. In contrast among the total group of pregnant patients 1.5 per cent had hemoglobin readings under 8.0 gm., 4.3 per cent were under 9, 11.6 per cent were under 10, 31.3 per cent were under 11, and 63.2 per cent were under 12 gm. In the group of private pregnant patients none had a hemoglobin less than 8 gm., only 1.2 per cent were under 9, 7 per cent were under 10, 25.9 per cent under 11, and 55.3 per cent under 12. Naturally, comparable figures were obtained for cell volume and cell count. While the difference between private and clinic patients is not a significant one, yet we believe that there are probable nutritional and hygienic factors in these anemias. There is no doubt that there is a significant difference between nonpregnant and pregnant patients and that pregnancy, in a corresponding stratum of patients, lowers the hemoglobin at least relatively.

One group of patients with anemia was given 5 gm. of ferrous carbonate daily, another group was given 5 gm. of iron ammonium citrate daily, another group was treated with blood transfusion, either after medication had failed or there was insufficient time before delivery for medication to have any effect. Other groups were treated with various other iron salts and with various proprietary

preparations, and lastly a control group was given no treatment. The period of observation and treatment with iron medication was at least four weeks and preferably twelve weeks. Due to the number of cases studied, and a small personnel, the follow-up was inadequate, and while there is a small number of carefully controlled patients, we do not believe that the results of treatment can be stated with certainty. There are sufficient data to indicate that it is extremely difficult to evaluate any medication over a period of weeks while the patient is pregnant because of the uncertainty of the normal curve of hemoglobin in pregnancy. We are discussing only the effect of treatment during pregnancy, because

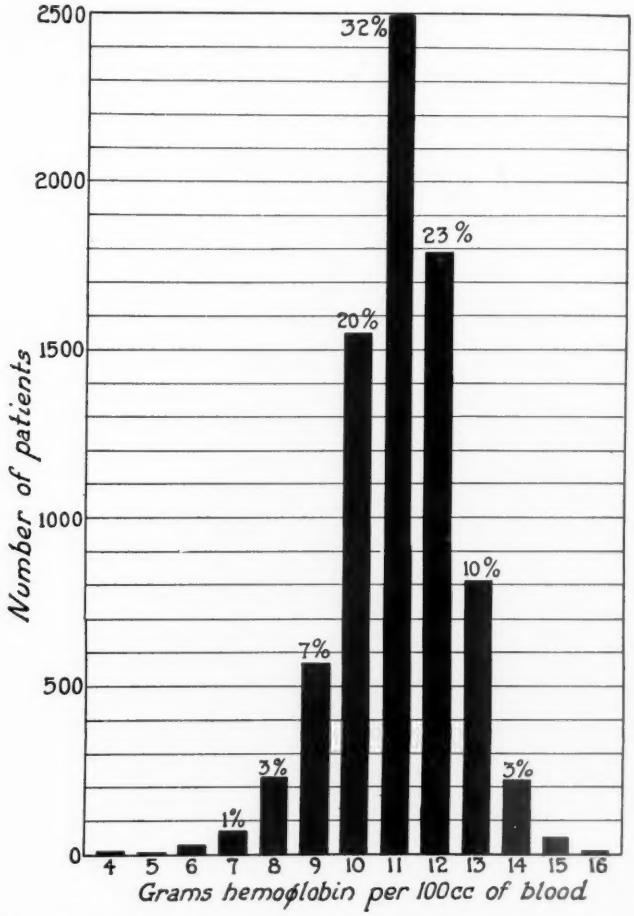


Fig. 2-A.—Graph illustrating the frequency distribution for hemoglobin (7,835 patients).

after delivery the hemoglobin will naturally tend to return to normal or the administration of iron will result in improvement in almost every case.

Table II lists the changes in hemoglobin concentration during pregnancy. The patients in column A were normal pregnant women; 9 out of 14 showed varying decreases in hemoglobin during pregnancy; 10 of these same patients without any treatment showed comparable increases after delivery of the same magnitude as the antepartum diminutions.

All other patients had a hemoglobin concentration of less than 9.0 gm. per 100 c.c. of blood on two occasions within a period of one to two weeks. Column B

indicates what happened to a group of anemic patients who had no treatment. Sixty-five patients showed varying amounts of increase in hemoglobin during pregnancy, 6 showed no change and 3 showed a still further reduction in hemoglobin. In 26 patients the anemia disappeared after delivery without treatment while 5 patients showed further decreases in hemoglobin.

Data from patients who received ferrous carbonate appears in Column C; from those who received iron ammonium citrate in D, and those who received a proprietary preparation which contained iron, liver, and vitamin B in Column E.

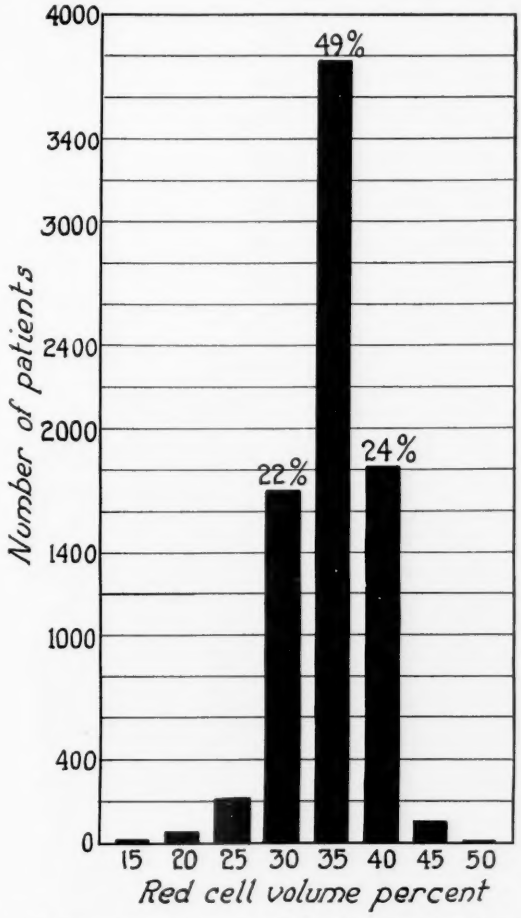


Fig. 2-*B*.—Graph illustrating the frequency distribution for cell volume (7,696 patients).

It is obvious that the majority of the patients in each group showed varying degrees of increase in hemoglobin concentration during pregnancy, a few showed a further decrease and some, especially those receiving ferrous carbonate, showed no change. *No significant differences in the increase of hemoglobin concentration in Columns C, D, and E as compared with B can be demonstrated.*

Column F contains data from a number of anemic patients who were transfused before delivery and others who were transfused after delivery. In both groups, but especially the latter, transfusion was necessary because treatment with iron salts had been of no value. Hemorrhage had not been the cause of

the anemia in the antepartum group but was the cause of a persistent anemia in several of the postpartum cases. It is evident that if an adequate amount of blood is given, a prompt and usually permanent increase in hemoglobin concentration occurs.

Studies of 79 cord bloods were made in cases where the maternal hemoglobin was or had been below 9.0 gm. during pregnancy. The means for this group for hemoglobin, cell volume and cell count were 16.21 gm., 53.85 and 4,128. The figures for a normal group of cord bloods were 16.81, 50.94, 4,488. There is no significant difference.

Fig. 4 contains essential data from patient No. 73027. The patient was thirty-four years old and had three living children. She had a severe secondary anemia of pregnancy. She received adequate amounts of ferrous carbonate and an anti-

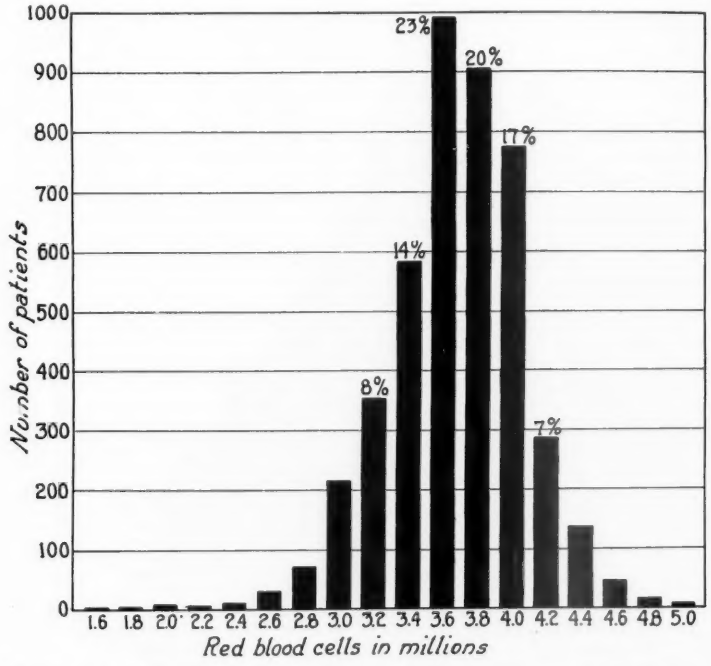


Fig. 2-*C*.—Graph illustrating the frequency distribution for erythrocytes (4,345 patients).

anemic diet. No increase in hemoglobin concentration occurred until after delivery. Iron metabolism studies showed a slight positive balance on diet but when ferrous carbonate was given the balance became negative. This patient had a color index of 1.05 to 1.17 and volume index of 1.20 to 1.26. The corpuscular volume was 104 to 108 cu. μ. Anisocytosis, poikilocytosis, and macrocytes were present throughout pregnancy. Her blood volume was always a low normal but what is of more importance the amount of hemoglobin per kilo was very markedly below normal. Repeated gastric analysis showed no free HCl in the fasting contents. After the injection of histamine a small amount of free HCl was present. The labor and delivery were uneventful. The baby weighed 3,985 gm. In view of the patient's age and the desirability of preventing further pregnancies and blood loss during menstruation, the uterus was removed. During pregnancy the iron content of the diet was sufficient for a positive balance but the fetal need of 4 or 5 mg. per day was lacking. On an intake containing 17 times the optimum

amount which was 20 mg. the patient was not in balance and the hemoglobin concentration did not increase. The infection had subsided before the latter study was started. There were repeated determinations of the iron balance but data from only three periods are given.

Fig. 5 contains essential data from patient No. 54736. She was twenty-five years old and this was her first pregnancy. She had been told seven years previously that she was anemic. She was admitted to the hospital because of diarrhea, abdominal cramps, vomiting, sore mouth, edema and anemia. Her color index was 1.06 to 1.14 and volume index 1.00 to 1.08. The corpuscular volume was

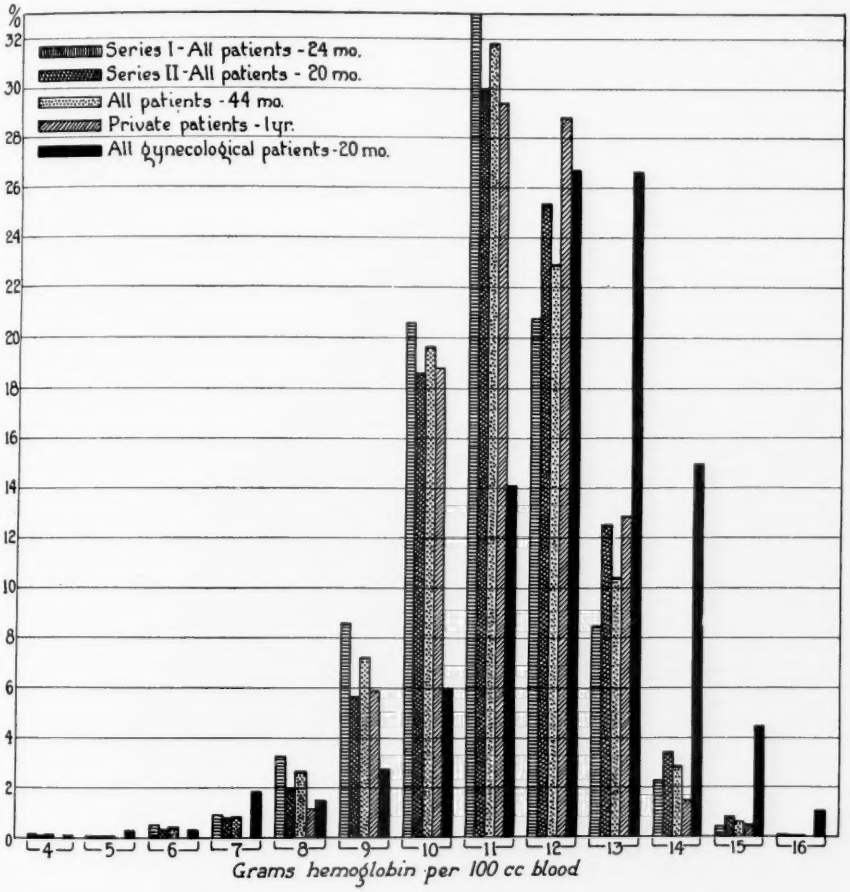


Fig. 3.—Graph illustrating the comparative frequency distribution for hemoglobin.

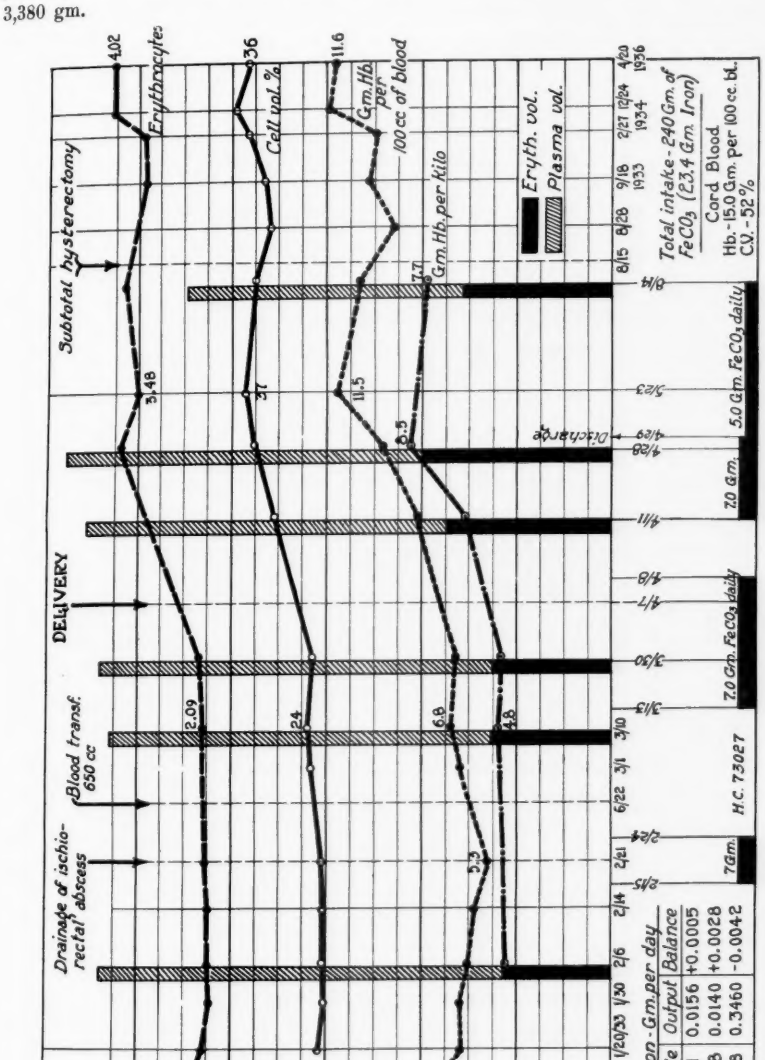
90 cu. μ. The usual type of abnormal cells were found. The hematologist was suspicious of a pernicious anemia but in view of free HCl in the fasting gastric juice, absence of neurologic findings and failure of parenteral liver extract to cause a characteristic increase in the reticulocytes, the final diagnosis was grave secondary anemia of pregnancy. The low blood volume and especially the very small amount of hemoglobin per kilo are noteworthy. She was given 4,600 c.c. of citrate blood over a period of twenty-three days. This was sufficient to raise the hemoglobin concentration and hemoglobin per kilo to normal, and give her a normal blood volume. She has never received any other antianemic medication and

TABLE II*

CHANGE IN HEMOGLOBIN GM. PER 100 C.C.	DIECKMANN-WEGNER NORMAL PREGNANT WOMEN				ANEMIA AND TREATMENT DURING PREGNANCY											
	A				UNTREATED B				FERROUS CARBONATE C		IRON AMMONIUM CITRATE D		LIVER IRON AND VIT. B E		TRANSFUSION INCREASE F	
	ANTEPARTUM		POSTPARTUM		ANTEPARTUM		POSTPARTUM								ANTE-PARTUM	POST-PARTUM
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	+
0.1-0.4		1		1	8	1		1	2		1					
0.5-0.9	1		2		15			1	3	1	3		1			
1.0-1.9	1	1	4	1	21	2	8	3	14	3	11	2	6		1	1
2.0-2.9	1	2	3		15		7		12		8		2		1	1
3.0-3.9		2		1	3		4		8		5		3		5	1
4.0-4.9		1			2		5		4		2		1		1	2
5.0-5.9		2	1		1		2								1	4
No change	2		1		6				13		3		4			
Total patients	14		14		74		31		60		35		17		9	9

*(+) indicates increase and (−) indicates decrease in hemoglobin concentration.

despite a slight polymenorrhea her hemoglobin has remained normal over a four-year period. She has been using contraceptive measures. The baby weighed 3,380 gm.



1933	No. of days	Iron - Gm. per day Intake	Output	Balance
2/6 - 2/11	5	0.0161	0.0156	+0.0005
3/6 - 3/11	5	0.0168	0.0140	+0.0028
3/11 - 3/15	4	0.3418	0.3460	-0.0042

Fig. 4.—Graph of patient with severe anemia of pregnancy who was treated with ferrous carbonate.

Many of the anemic patients were edematous during the latter part of pregnancy but it was only in four patients that there seemed to be some connection between the anemia and the edema and albuminuria. Two of these were admitted to the hospital for cardiac decompensation. After an adequate amount of blood was given to raise the hemoglobin to normal, the edema, albuminuria and cardiac

symptoms and signs disappeared and the remainder of the pregnancy was uneventful in three. Two patients were subsequently delivered of twins. The fourth patient had a premature delivery of a macerated fetus three months after the transfusion. Three years later she again had a premature stillbirth in another

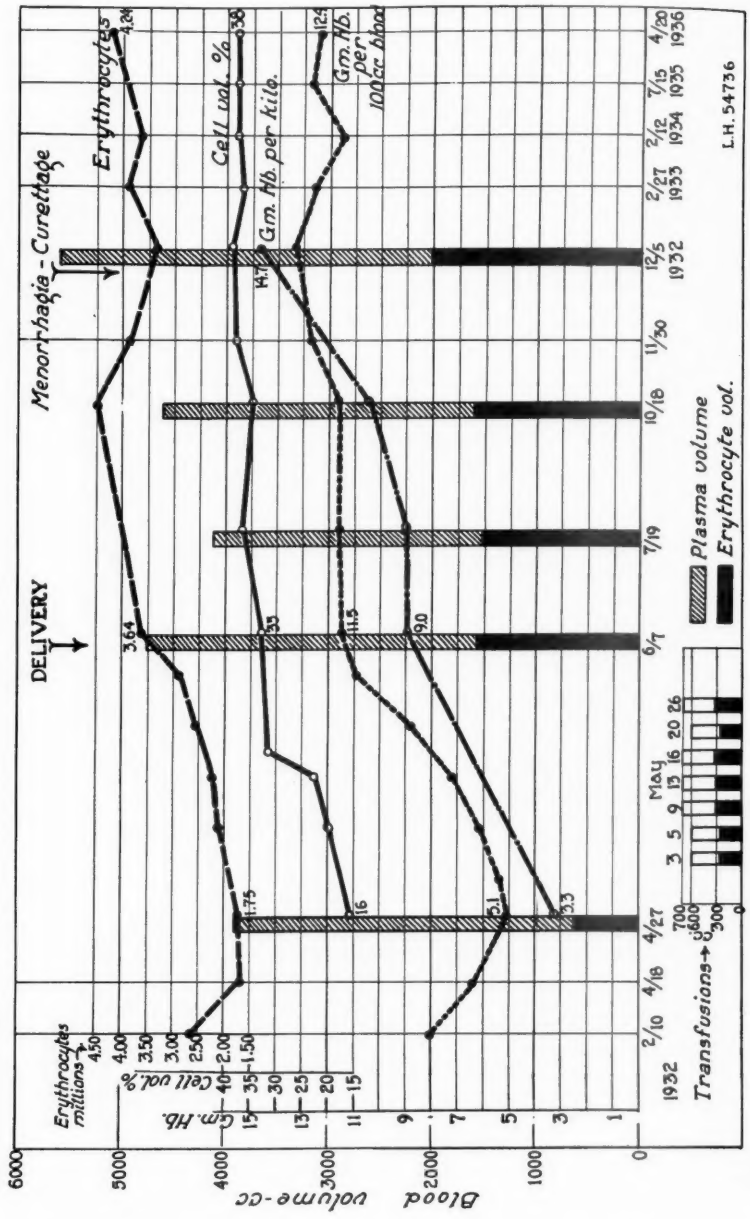


Fig. 5.—Graph of patient with severe anemia of pregnancy who was treated with blood transfusion.

hospital and when seen four months postpartum had a hemoglobin of 6.8 gm. per 100 c.c., cell volume of 28, and cell count of 3,840,000. She states that there was no appreciable hemorrhage. Consequently the pregnancy may have caused the anemia which in turn may have produced the premature labor.

Dieckmann has given the following average figures for the hemoglobin concentration of 38 patients with preeclampsia as 12.9, for 59 patients with vascular-renal disease as 13.2, and for 34 patients with eclampsia as 14.9 gm. per 100 c.c. The average figures for the cell volume are 38.6, 40, and 45 volumes per cent, respectively. While these figures may be higher than they should be because of the blood concentration found in preeclampsia and eclampsia, yet they indicate that the majority of the acute toxemias of pregnancy seen by us are not due to or associated with an anemia.

There were 906 patients with anemia over a period of three years eight months. Only 2 deaths occurred during this period in which the chronic anemia was a possible factor. Both patients had edema, albuminuria, dyspnea and weakness, and in both these symptoms were attributed to cardiac decompensation. Post-mortem examination revealed that one did have cardiac disease but the other autopsy did not show any pathology sufficient to account for death. The pathologist noted in both cases that the tissues contained less blood than normal.

DISCUSSION

Many obstetricians have stated that chemical analysis of the blood in pregnancy is of little value. The importance of at least one application of chemistry to obstetrics is illustrated by the fact that chemical determination of hemoglobin, a complex chemical compound, indicates that 63 per cent of our pregnant women are anemic according to nonpregnant standards.

Our data indicates that the concentration of hemoglobin, the cell volume and the erythrocyte count are definitely decreased during pregnancy and that the normal standards for the nonpregnant differ from those of the pregnant women. Our average figures are slightly less than those of Dieckmann and Wegner, and Kühnel, because patients with marked anemia are included in our tables. Statistically the minimum figures in normal pregnancy should be 10.16 for hemoglobin, 33.11 for cell volume and 3.36 for erythrocyte count.

Dieckmann and Wegner postulated that the decrease in the erythrocytes was a part of the mechanism by which the viscosity of the blood was lowered. This phenomenon, according to them, in combination with an increase in the blood volume corresponding to an increase in weight, a decrease in serum protein concentration and increase in cardiac output are necessary for the gaseous metabolism of the fetus and also of the maternal tissues and tend to minimize strain on the cardiovascular system of the mother.

The physiologic decrease and increase in hemoglobin, cell volume and erythrocytes during pregnancy have not been properly evaluated by investigators. The fact that the hemoglobin concentration can increase 2, 3 or even 6 gm. within four weeks without treatment at once casts doubt on any reports which state that improvement occurred during pregnancy when iron salts were administered.

It is our belief that the hemoglobin concentration of the cord blood is usually normal even though the mother has an anemia, but in a num-

ber of instances the hemoglobin concentration has been definitely below normal. This is especially important in view of the fact that milk contains little iron and if the baby begins life with a low concentration of hemoglobin, anemia is quite likely to develop. Recognition of the above is most important in premature infants because they are born without the storage of iron in the liver which exists in the term baby. Furthermore severe anemia predisposes to premature delivery.

Transfusion of blood, if properly supervised and if adequate amounts are given, has always been efficacious in raising the hemoglobin concentration and relieving all symptoms and signs of anemia. Deleterious effects on mother and baby have not been observed and premature labor was in no case initiated.

A number of iron metabolism studies have been made in both nonpregnant and pregnant individuals. Farrar and Goldhamer kept two subjects in a positive balance on a daily intake of 5.2 and 7.8 mg. of iron, respectively. The period of study was 316 and 260 days, respectively. Females require more iron because at least 12 mg. of iron are lost in the form of hemoglobin during each menstrual cycle. Ohlson and Daum report that an average daily intake of 13.8 mg. of iron resulted in a negative balance.

Coons and coworkers have reviewed and studied the iron metabolism during pregnancy. They have shown that with an average daily intake of 14.72 mg. there will be an average positive daily balance of 3.16 mg. A 3,100 gm. fetus will contain approximately 375 mg. of iron. The fetal need for iron first becomes noticeable at twenty weeks, but it rapidly increases and at term it requires 8 mg. per day. During the last trimester of pregnancy the average daily requirement for the fetus is 4.7 mg. Coons concluded that "iron retention was found to be quite deficient in this series of metabolic studies. There were no negative balances but approximately three-fourths of the number fell short, many of them far short of the estimated fetal need. The low retentions were not due to *low total iron intake but probably to a deficiency of other dietary factors which promote the utilization of iron.*"

It is obvious that if the cause of the anemia occurring in pregnancy is merely a lack of iron in the diet then these patients who receive iron should all show rapid improvement if adequate amounts of iron are added. The fact that a considerable number of patients show no improvement indicates that some other substance is lacking or that the iron is not being absorbed or that if absorbed it is not being utilized.

CONCLUSIONS

The means for the hemoglobin concentration in pregnancy are 11.56 gm. per 100 c.c. of blood, for the cell volume 37.31 volume per cent, and for the erythrocyte count 3.77 million.

The minimum standards for normal pregnancy are 10 gm. of hemoglobin per 100 c.c. of blood, 33 volumes per cent for the cell volume, and 3.36 million for the erythrocytes.

Eleven and six-tenths per cent of our pregnant patients have an anemia, according to our standards, but if the standards for the nonpregnant patients are used 63.2 per cent must be classed as anemic.

A normal decrease and increase in the hemoglobin, cell volume and erythrocyte count occurs during pregnancy. These changes cannot be altered by treatment. The fluctuation may amount to 2, 3 or even 6.0 gm. of hemoglobin within a period of four to six weeks.

Knowledge of these marked fluctuations should make one particularly cautious about attributing an increase in the hemoglobin concentration, cell volume and erythrocyte count to any previous therapy.

An adequate amount of transfused blood will raise the hemoglobin concentration to normal permanently and relieve all the symptoms and signs of the anemia.

Blood transfusion during pregnancy, if done properly, has no deleterious effect on the mother or the fetus. It has not caused premature labor.

The prevention of anemia of pregnancy is easier than the cure. An adequate diet, with proper hygiene, is the best prophylaxis.

A normal hemoglobin content is essential for the normal function of the organs of the body. Toxemia is less likely to occur, the patient is better able to tolerate blood loss and the strain of labor, her tissues have more resistance, she is less likely to become infected, and her recovery after delivery is more rapid.

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DISCUSSION

DR. FRED L. ADAIR, Chicago, Ill.—Dr. Dieckmann and Dr. Grant have carried on most of the detail work in connection with this study which had as its fundamental concept the idea that there were certain physiologic changes in the blood during pregnancy which indicated an anemia. We were dealing in many cases with an anemia which was not a true anemia and certain standards had to be established which were somewhat different from those for the nonpregnant woman. We have attempted to follow patients on a higher economic level, who it was supposed had better hygienic conditions than our other patients. We also used as a control

group the gynecologic cases. I would like to stress the fact that we were dealing with all gynecologic conditions, and in spite of many cases that had definite secondary anemia from uterine bleeding, there was still a significant difference between the blood condition of these and the pregnant patients. We distinguished, then, between what may be called a physiologic or a relative anemia and an actual anemia which unquestionably does exist in some of the pregnant women.

Now, so far as to what constitutes actual anemia we believe that the standard for pregnant women should be a gram or more lower than for the nonpregnant. In other words, if you assume that 12 gm. is the normal limit, you should probably take 10 or 11 gm. as the lower limit for pregnancy. On this basis we found that in our private patients only 7 per cent had a hemoglobin below this level of 10 gm., whereas in the clinic cases there were 12 per cent. We assume the discrepancy is largely due to the difference in hygiene and in nutrition. According to our observations so far, diet and hygiene are of far more importance than any medication that can be given.

Among all of our gynecologic patients, which include some with genital bleeding, we find that 74 per cent had a hemoglobin of 12 per cent or above. If we include all cases, only 37 per cent were over 12 per cent, so that there is a very significant difference in the hemoglobin. Then, if we take the private prenatal cases, we find that 45 per cent were over 12, whereas in the clinic cases 37 per cent were over 12. We conclude, therefore, that so far as anemia is concerned there is first, a physiologic condition of the blood which simulates anemia in the nonpregnant woman; second, that our private patients have less actual anemia than clinic patients; third, that nonpregnant women show an actual anemia less frequently than the pregnant women, due to the different accepted standards.

We also made a study of the fetal blood. Apparently the fetus has few iron requirements until after twenty weeks of gestation, after which time the daily requirement for iron gradually increases until at term it reaches a point of 8 mg. We would say, then, that prior to twenty weeks of gestation the demand on the part of the fetus for iron is not appreciable. We studied fetuses born of mothers with anemia, taking 6, 8, and 9 gm. as a basis for our estimate. The average hemoglobin in these cases was 16.2, the erythrocyte count reading a little less than a quarter million. In the control cases we found that the hemoglobin readings were essentially the same, 16.8 as compared to 16.2; the erythrocyte reading was a little less than four and a half million, showing a little higher hemoglobin reading in the control series and a little higher erythrocyte count. Probably the hematocrit reading was a little higher than the erythrocyte reading and the hemoglobin.

We feel, then, that the anemia condition in the mother has little influence on the fetus so far as the blood findings are concerned. If the fetus is born prematurely it has a relatively small amount of iron, whereas the full-term fetus has stored considerably more iron. We believe from these observations that most of the iron supply takes place in the last six weeks. This is undoubtedly a handicap for the premature fetus.

DR. EVERETT D. PLASS, IOWA CITY, IA.—I would like to ask whether the authors feel that there is any relationship between the amount of protein in the diet and the tendency of pregnant women to develop anemia?

DR. DIECKMANN (closing).—In reply to Dr. Plass, we cannot state definitely but we believe that diet is the prime factor in the anemia of pregnancy. Certainly this is true in the anemias which occur in India, and as Dr. Adair emphasized, the difference between our ward and private patients is probably due to the difference in diet. The important part of the diet being the protein which, of course, unfortunately is the more costly of the various foods.

A FURTHER STUDY OF EXTRAPERITONEAL PELVIC CONDITIONS IN WOMEN

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EXTRAPERITONEAL pelvic conditions, although not of frequent occurrence, are met with sufficiently often to deserve more attention than is usually given them. In 1930 I published an article on this group of lesions and today I shall discuss this subject more thoroughly, adding to the series reported in the first paper some cases seen since 1930 which demonstrate additional types of extraperitoneal pathology.

It is needless to say that the general and surgical treatment should be different for extra- and intraperitoneal conditions and that failure to appreciate this fact may result disastrously for the patient. It does, however, seem worth while to stress the difficulty of determining in some instances the relationship of a pelvic lesion to the peritoneal cavity, and that because of this difficulty mistakes in diagnosis can easily be made.

Abscesses are the extraperitoneal pelvic lesions that most frequently call for surgical interference. They usually develop as a result of a parametrial infection. Mauriceau, in about the middle of the eighteenth century, described inflammation of the pelvic connective tissue, but it was Virchow who first used the term parametritis to denote inflammation occurring in the pelvis outside of the peritoneum.

Parametritis includes exudates in the pre- and retrocervical tissues, but it is the intraligamentous infiltrations in the base of the broad ligament which are most commonly seen, and which, when suppuration occurs, form the broad ligament abscesses. It is difficult to accurately determine the incidence of parametrial infection, for in mild cases patients may have a moderate elevation in temperature for only a few days, and examinations show nothing more than slight pelvic tenderness. The mild infections are of limited clinical interest for they usually clear up without any particular treatment, but it is very important to recognize promptly the extraperitoneal pelvic abscesses which develop from the more severe types of parametrial infection.

Since 1900, 53 women with extraperitoneal pelvic abscesses have been treated in the Johns Hopkins Hospital, which means that about once in every eight months we see a patient with this condition. Thirty-four of these 53 cases were on the gynecologic service, 19 on the obstetric. Forty of the women were white, 13 colored. When one considers that the relative number of white and colored patients admitted to the hospital is about three to one, it would seem that extraperitoneal abscesses occur with equal frequency in the two races.

Of the 53 extraperitoneal abscesses, 50 were located in the broad ligaments. The other 3 developed in the connective tissue in front of the cervix, 2 of them pointing in the subcutaneous tissue of the midportion of the lower abdominal wall, the third localizating directly under the bladder. In this series, there were no true instances of extraperitoneal abscesses arising behind the cervix, although in several cases suppuration started in one or both broad ligaments and then extended downward and medially toward the retrocervical tissue. Of the 50 broad ligament abscesses, 25 were on the right side, 21 on the left. In 4 instances the infection was bilateral, suppuration developing in both broad ligaments.

TABLE I. ETIOLOGIC FACTORS IN 53 CASES OF EXTRAPERITONEAL ABSCESS IN WOMEN

18	followed abortions.
	In 7 of the 18 the abortions were induced by the patient or abortionist.
	In 3 the placenta had been removed manually by the family doctor.
	In 2 a curettement had been done at home by the family physician.
	In 1 a deep cervical tear had occurred at the hands of the family doctor.
	In only 5 was the abortion uncomplicated by other factors.
18	followed normal pregnancies but only 6 of the women were delivered by the hospital staff.
11	followed instrumental or operative deliveries.
	In 3 of these 11, forceps had been used in the patient's home by the family doctor.
	In 1 a curettement had been done in the patient's home by the family doctor.
	In 1 the uterus had been packed by the family doctor because of inversion.
	In 1 a forceps delivery was done at the hospital.
	In 1 a hysterectomy for placenta previa was performed.
	In 1 a craniotomy on a dead child was performed.
	In 1 a version and extraction were performed on an eclamptic infected woman.
	In 2 cervical cesarean sections were performed on infected women.
1	followed a gynecologic operation for dermoid cyst.
1	followed an infection of the vulva and was probably gonorrheal in origin.
4	cases only gave no history of a recent pregnancy, operation or infection.

A consideration of the etiologic factors in this series of extraperitoneal pelvic abscesses is of interest. One case developed after a gynecologic operation for a dermoid cyst, another followed an infection of a bartholinian gland in a woman from whom the uterus, both tubes and ovaries had been removed several years previously. This is the only instance of a gonorrheal extraperitoneal pelvic abscess of which we have any record in the hospital. A definite history of a recent abortion or pregnancy was obtained in 47 of the 53 cases. In 24 of these the pregnancy had been complicated by either an instrumental or operative delivery or had been terminated by the abortionist.

Of the 47 patients with a history of a recent pregnancy or abortion, only 12 had been taken care of by the hospital obstetric service, and in 6 of these, because of obstetric complications, an operative or instrumental delivery had been necessary, even though several of these women were already infected on admission to the hospital. Since 1900, 36,000 women have been delivered by the obstetric service and, as has just been pointed out, only 6 of this group of women developed broad ligament abscess. This gives us an idea as to how seldom this complication follows normal properly conducted deliveries. Table I shows graphically the etiologic factors in this series of cases.

The onset of symptoms after delivery varied from three to fourteen days but many of the hospital records of the earlier cases do not give exact information on this point. Every one of the 53 women in this series complained of lower abdominal pain, and about half of them gave a history of chills. Gastrointestinal symptoms occurred somewhat rarely. In only 9 cases was there a history of vomiting before operation. In many cases the patient had had such profuse uterine bleeding following an abortion or full-term pregnancy that a marked secondary anemia was present. In fact, the average hemoglobin estimation was only 60 per cent, with readings in some cases as low as 28 and 26 per cent.

Nine patients complained of severe pain on walking, and when admitted to the hospital showed a definite limp. In these cases there was limitation of motion of the hip, the patient holding the thigh flexed and adducted. This is due to a spasm of the psoas muscle and may mislead one into thinking that he is dealing with a tuberculous abscess arising in the vertebrae or hip joint. On the other hand, this limitation of motion of the thigh may help the surgeon to recognize that a pelvic lesion is outside of the peritoneal cavity.

Most of the patients appeared quite ill on admission. The average temperature was 103° and in many cases readings of 105° were recorded. In only a few instances did it fail to reach 101°. The pulse rate corresponded with what would be expected with the elevation of temperature. The leucocytes ranged from 9,000 to 45,000, with most of the patients having a white count of 20,000. Usually the leucocyte count was highest when the temperature was high, as exemplified by a case in which the temperature was 105° and the white count 45,000. Occasionally, however, there were exceptions to this rule, as shown by one of our patients who had a temperature of only 100° and a white count of 26,000. Incidentally this woman was very ill although eventually she recovered.

Tenderness was elicited in every case on palpation of the lower abdomen. An abdominal mass was found in 41 of the 53 cases. In all except the three cases of precervical infection these masses were situated in one or both quadrants of the abdomen just above Poupart's ligament. The size of the mass varied considerably; in some instances merely an indefinite induration was felt, while in others a stony hard tumor extended upward from the inguinal ligament to the level of the umbilicus. The sixth was the earliest day after delivery on which one of these extraperitoneal masses was felt on abdominal examination.

On vaginal examination, in 27 cases definite masses were found in the base of the broad ligaments. In nine others some pelvic induration was made out. Nine patients showed only moderate tenderness, while in three the pelvic examination was recorded as being entirely normal. In these three latter cases, the extraperitoneal pelvic conditions were diagnosed entirely on the history and abdominal examination.

In cases with a characteristic history and typical physical findings, the diagnosis of extraperitoneal pelvic abscess is comparatively easy so long as one bears constantly in mind the thought that some of the pelvic infections in women are extraperitoneal. For instance, there is no excuse for missing the diagnosis in a woman who gives a history of an induced abortion with the later occurrence of chills, fever, and pains in the lower abdomen and on whom abdominal palpation reveals a tender mass just above Poupart's ligament, while pelvic examination shows induration high in the vagina.

However, in some of the patients with extraperitoneal pelvic infections most of the symptoms and signs that we associate with this condi-

tion are lacking, and mistakes in diagnosis can easily be made. For instance, in this series of 53 extraperitoneal pelvic abscesses, 6 were incorrectly diagnosed and as a consequence the treatment the patients received is open to criticism. When one considers that some of the earlier cases occurred in the hospital twenty-five or thirty years ago and that this report is based on the work of 14 different gynecologists and 6 obstetricians, we feel that there is little cause to apologize for our statistics, and yet in order to stress the importance of correctly diagnosing extraperitoneal pelvic lesions we are emphasizing not the 47 cases correctly diagnosed, but the 6 in which the extraperitoneal character of the infection was not recognized.

In 2 of the 6 cases incorrectly diagnosed, the patients did have some mild salpingitis, but the main pathology was extraperitoneal, and the surgeon would have exercised better judgment if he had stayed out of the peritoneal cavity. In the other 4, the peritoneum, uterus, tubes, and ovaries appeared perfectly normal when the abdomen was opened, although large extraperitoneal broad ligament abscesses were present. While we regret these mistakes in diagnosis, these last 4 cases gave us the opportunity of definitely proving that inflammation of the pelvic connective tissue is not always accompanied by inflammation of the pelvic peritoneum, as has been stated by some of those who have written on this subject.

Fifty-one of the 53 patients who had extraperitoneal abscesses were operated upon, and upon leaving the hospital were free from symptoms, the abscess having been evacuated. In 12 cases nonoperative treatment was tried even though the diagnosis of an abscess had been made. Rest, douches, and repeated transfusions were prescribed, but 10 of these 12 finally came to operation. Two patients did leave the hospital without operation, but although the temperature was normal on discharge, abdominal masses were still palpable above Poupart's ligament, and vaginal examination showed induration at the base of the broad ligaments. These two patients were under our care in 1920 and 1922, and although a special effort has recently been made to locate them, the attempt has been unsuccessful, so we do not know how they have fared. Probably they had further trouble.

Not one of the 51 women treated surgically died, although many of them were very ill when operated upon. When discharged, they were symptom-free, and on most of them the abdominal and pelvic examinations were essentially negative. In view of this, we feel that extraperitoneal drainage is the procedure of choice in all cases of extraperitoneal pelvic abscess, even though these two patients did leave the hospital without operation and with normal temperatures.

Because of mistakes in diagnosis, the peritoneal cavity was opened in 6 cases. These mistakes have been noted before, but we are mentioning them again in order to discuss the operative procedure carried out after the surgeon had opened the peritoneal cavity. In four instances the operator incised the peritoneum covering the broad ligament abscess and drained the extraperitoneal condition through the peritoneum. These patients were very ill after operation, but finally recovered. In the other 2 cases the surgeon closed the peritoneum without drainage, made an inguinal incision down to the broad ligament abscess, and drained the condition

extraperitoneally. These 2 patients had a rapid and uncomplicated convalescence. In our opinion, better surgical judgment was exercised in the handling of these two latter cases.

Most authorities believe that an anterior vaginal incision is indicated in the rare instances in which pus has collected under the bladder, and that the abscesses which develop in the subcutaneous tissue of the mid-portion of the lower abdomen are best treated by a lower midline extraperitoneal incision. However, there is still some difference of opinion as to which is the best method of draining broad ligament abscesses which are the suppurative extraperitoneal lesions most frequently encountered. Some operators attempt to reach them through the vagina, using the following technic: An incision is made posterior to the cervix such as is used in draining an intraperitoneal abscess. The peritoneum must not be opened but pushed gently back with the finger. A blunt artery forceps is then wormed upward and laterally toward the involved broad ligament.

In discussing such an operation, it must first be pointed out that it is beset with several dangers. If the forceps happen to pierce the peritoneum covering the indurated broad ligament, it will emerge into the peritoneal cavity and quite likely infect it with the organisms which up to that time had been walled off in the broad ligament. Moreover, in tunneling the instrument laterally toward the broad ligament there is distinct danger that the operator may injure the ureter or uterine artery, as the instrument must pass very close to these structures.

This method of vaginal drainage was attempted in 7 of the 48 patients with broad ligament abscesses that were treated surgically. In 3 of these, the attempt to reach the pus from below was entirely unsuccessful and an extraperitoneal inguinal incision was later necessary. The 4 other patients recovered after drainage through the vagina, but their postoperative stay in the hospital averaged forty-seven days.

A second method of draining broad ligament abscesses extraperitoneally is by what is sometimes called the inguinal route, as shown in Fig. 1.

T. S. Cullen, in an article published in 1917, so clearly described this operation that I shall quote directly from his paper, "A gridiron incision is made above and parallel to Poupart's ligament and the fascia and muscles are split, as in an appendix operation. As soon as the peritoneum is reached, it is pushed toward the median line but without being opened. The two index fingers then gradually spread the broad ligament until the area of induration is reached." Thirty-seven patients in this series were operated on by this method. They all recovered in an average time of twenty-nine days, or eighteen days less than those patients whose broad ligament abscesses were drained through the vagina.

It is of interest that the different surgeons who have had charge of the patients in this series of cases have not agreed as to how soon sur-

gical intervention should be carried out in cases of broad ligament abscess. Most of them have felt that as soon as the diagnosis is made, inguinal extraperitoneal drainage should be instituted, but a few have delayed operation until the inguinal mass felt upon abdominal palpation had reached considerable size and preferably until it had caused bulging of the overlying skin. This latter group of men have contended that by this delay the pus becomes more accessible and that the danger of opening the peritoneal cavity is lessened.

A study of our records has not borne out these claims, for the ten patients whose operations were delayed after diagnosis was made averaged seven days longer in the hospital postoperatively than those operated upon at once, in addition to the two weeks before operation that they

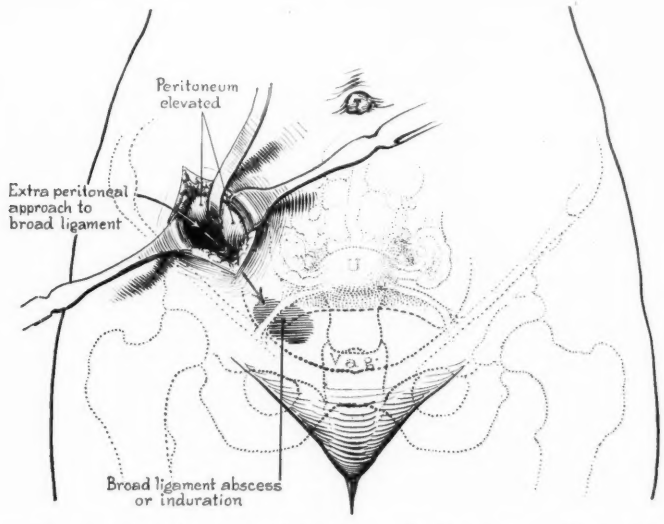

Fig. 1.—The easiest and most satisfactory method of approaching a broad ligament abscess. A gridiron incision is made above and parallel with Poupart's ligament. As soon as the peritoneum is reached, it is pushed toward the median line without being opened (after Cullen).

had spent waiting for the abscesses to become large, making their entire convalescence three weeks longer than that of the patients operated upon promptly. Moreover, the only instance of accidental opening of the peritoneal cavity occurred in one of the ten cases in which inguinal drainage was delayed for two weeks after the diagnosis had been made. Fortunately, no serious consequences followed this operative accident.

Cultures were taken in 33 of the 53 patients on whom operations were performed. Positive growths were obtained in 22 instances; in 11 the cultures were reported to be sterile. The streptococcus was the organism most commonly found, being grown in 11 cases. The staphylococcus came next. It was cultured from five patients. *B. proteus*, the pneumococcus, and a diphtheroid organism were each cultured once.

The colon bacillus was not grown in pure culture from a single case, but it was found three times as a secondary invader, twice along with the streptococcus and once with the staphylococcus. In 8 of the 14 cases in which the streptococcus was the offending organism, the type was not mentioned. Four times it was reported to be the hemolytic variety, once the nonhemolytic, and once it was found to be anaerobic. It has been only in recent years that, largely due to the work of Schottmüller, our attention has been directed to anaerobic organisms in puerperal infections, and special methods have been employed to grow them, so it may well be that they were present in some of the earlier cases of our series in which the cultures were reported as sterile. Incidentally, in 1929, Harris and H. Brown, in their study of 113 cases of streptococcic puerperal infections, found the anaerobic with approximately the same frequency as the aerobic variety, and Schwarz and T. K. Brown have in a recent issue of the *American Journal of Obstetrics and Gynecology* stressed the importance of anaerobic streptococci.

The quantity of pus found at operation varied from an ounce to a quart. The speaker had gathered the impression from some of the literature that in broad ligament abscesses the pus is usually thin and watery in character so he was rather surprised to find records of it being thick in eleven cases, foul smelling in eight and yellowish green in seven. In four of the cases from which thick foul smelling pus was evacuated the cultures showed no growth. Fisher and Abernathy have recently stressed that the anaerobic streptococcus can often be found in various putrid and gangrenous lesions throughout the body, and this if of interest to us, for it supports the idea already mentioned that anaerobic organisms were probably present in some of our earlier cases in which the laboratory methods then used failed to show the presence of any bacteria.

There was no operative mortality in this series of cases. As has been said, the patients on whom the broad ligament abscesses were drained by the inguinal route left the hospital in twenty-nine days after operation, while those on whom the inflammatory condition was approached through the vagina had a postoperative convalescence of forty-seven days, or eighteen longer than the first group.

We have recently endeavored to trace all of the 53 patients who had extraperitoneal abscesses but, frankly, this attempted follow-up has not been very successful. When one considers that it has now been thirty-five years since the first of these women was operated upon and that most of them belonged to the dispensary class of patients who change their residence every few years, this is understandable though disappointing. Still we have in the past few months traced 17 of the 51 patients operated upon, and while this means that we know about the present health of only one out of every three women in this series, a study of the histories obtained from even this small group of patients has brought out interesting facts. Six of the 17 women have had one or more children since leaving the hospital, which seems

to represent about the normal fertility for such a group of women and indicates that extraperitoneal pelvic infections seldom cause sterility. Two women became pregnant within six weeks after leaving the hospital. Apparently it is dangerous for a woman to conceive immediately after she has had a broad ligament infection, for both of the patients who became pregnant so soon after leaving the hospital had uninduced abortions and were readmitted with severe puerperal infections. One of these died from a streptococcal septicemia, and the other recovered only after a long illness. It is of interest that neither of these women on their second admission to the hospital showed any evidence of a localized infection either in the parametrium or pelvic peritoneum. One would suspect that some organism had remained viable in the broad ligament after the patient left the hospital and that they were stimulated to activity by the occurrence of conception so soon after the original infection. These two patients are the only ones that we know of in the entire series whose health after they left the hospital was influenced by a preceding extraperitoneal pelvic infection. Among the group of women who we know have enjoyed good health since their operations are the first two women in this series who were operated upon thirty-five years ago, and who are now both sixty-eight years old.

In summary, this study of extraperitoneal pelvic abscess has brought out these facts:

1. The great majority of cases follow induced abortions or operative deliveries on infected women.

2. A history of lower abdominal pain, chills and excessive bleeding is usually obtained. Few patients complain of gastrointestinal symptoms.

3. Some of the patients complain of pain on walking and hold the thigh flexed and adducted. This finding may be of help to the physician in recognizing that he is dealing with an extraperitoneal pelvic lesion. It is due to spasm of the psoas muscle.

4. In a typical case the temperature and leucocyte count are both high and the examiner can demonstrate abdominal and pelvic tenderness, induration high in the vagina and an abdominal mass just above Poupart's ligament.

5. In many cases the history and physical findings are not typical, and it is easy for the surgeon to mistake a broad ligament abscess for an intraperitoneal condition.

6. All extraperitoneal infections should be drained extraperitoneally.

7. Better results are obtained by draining broad ligament abscesses extraperitoneally through a low McBurney incision (the inguinal route) than by attempting to drain them through the vagina without entering the peritoneal cavity.

8. Extraperitoneal drainage should be instituted as soon as the diagnosis is made. There is no advantage in delaying the operation until the inguinal mass becomes larger.

9. The streptococcus is the organism most frequently cultured from extraperitoneal pelvic infections. Probably in many of the cases in

which the cultures were reported negative, anaerobic streptococci were present, and if special culture methods had been used, positive bacterial growths would have been reported.

10. The pus in many cases of broad ligament abscess is not clear and watery, as might be expected, but thick, yellow and foul smelling.

11. Although many of the patients were desperately ill when operated on, there was no operative mortality in this series of cases. All of the women operated on left the hospital apparently well.

12. Extraperitoneal pelvic infections do not decrease fertility, but there seems to be danger for a woman who has had a broad ligament abscess to become pregnant at once, for in this series the two women who conceived six weeks after leaving the hospital both had puerperal septicemia from which one of them died.

13. Except for the danger associated with conception following immediately after operation, broad ligament abscesses do not apparently affect the health of the patient after the pus has been evacuated and the temperature has returned to normal.

There are in addition to the parametrial abscesses just described other conditions such as myomas and hematomas, which are occasionally seen in the broad ligaments. The treatment of the psoas abscesses due to disease of the spinal column and the pelvic bones belongs to the orthopedic surgeon, but there is a group of psoas abscesses originating in pathologic conditions outside of the bones which may offer diagnostic difficulties to whoever sees them, whether he be orthopedist or gynecologist. These lesions have been discussed by Baer, Bennett and Nachlas in an article on "Non-Spinal Psoas Abscess." As they point out, a suppurative myositis of the posterior abdominal wall, whether it be the result of a metastatic infection or the result of an infected hematoma following trauma, will find in the sheath of the psoas muscle the course of least resistance for the discharge of its pus. Moreover, infections of the kidneys and also those starting in the solid and hollow viscera may cause such abscesses. Then, too, suppurative conditions both tuberculous and nontuberculous sometimes arise in the retroperitoneal lymph glands and the pus may travel along the same path as that taken by a tuberculous abscess arising from one of the vertebrae. Usually these nonspinal psoas abscesses point below Poupart's ligament, while the puerperal broad ligament infections point above it, but despite this fact the two groups of cases may be confused unless the strictest attention is paid to both history and physical examination.

I should like to present brief summaries of four cases taken from my own practice, which demonstrate unusual extraperitoneal pelvic lesions which are of some interest because of their rarity. The first is that of a forty-three-year-old woman who complained of a hard lump in the lower abdomen, which extended in the

midline from the symphysis pubis to within two centimeters of the umbilicus. Since on vaginal examination the abdominal mass could not be differentiated from the uterus, it was thought that we were probably dealing with a myomatous uterus. A lower abdominal midline incision was made and we were surprised to find that the tumor was outside the peritoneal cavity, although lying under the recti muscles. It extended from the region of the bladder to within a few centimeters of the navel as is shown in Fig. 2. The bladder and the recti muscles were not adherent to the

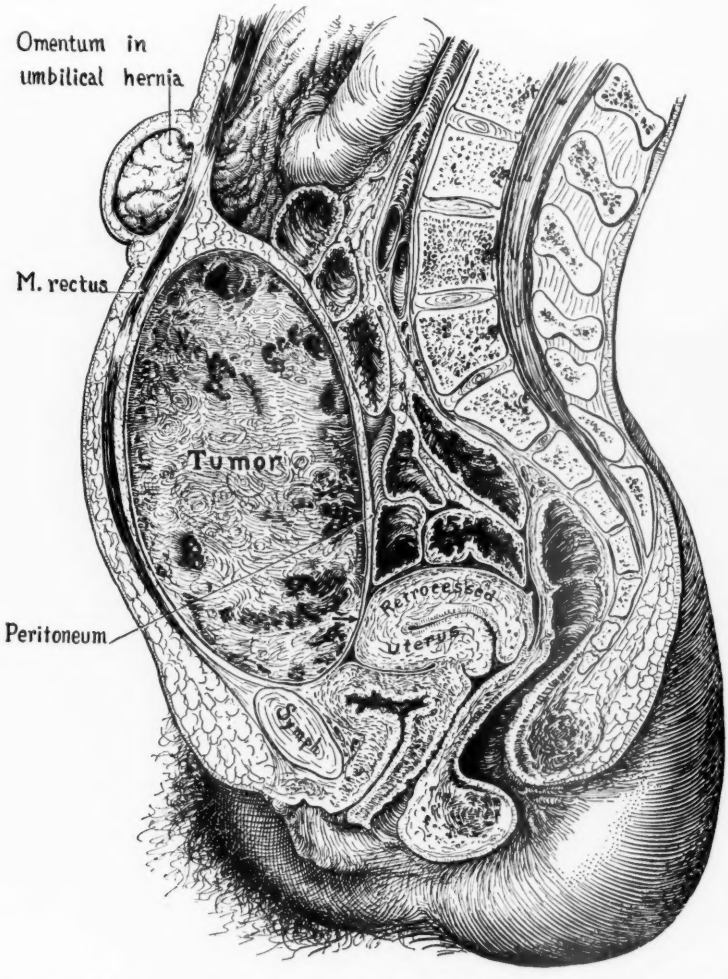

Fig. 2.—Urachal myoma showing its size and position in the properitoneal tissue, between the rectus muscles and the peritoneum.

tumor. It was not necessary to open the peritoneal cavity to remove this growth, but because of a large umbilical hernia, the peritoneum was afterward incised. The uterus contained no fibroids. It was normal in size and appearance as were also the fallopian tubes and the ovaries. The tumor weighed 600 gm., it measured 14 by 10 by 9 cm. There was no pedicle leading from the tumor. The cut surface presented the whorllike appearance of a myomatous growth. Scattered through the firm opaque grayish white tissue were islands of semisolid, spongy, translucent material, such as

is associated with the hyaline degeneration of a myomatous growth. The microscopic sections showed muscle tissue with, in places, considerable hyaline degeneration. There was no evidence of malignancy. A diagnosis of fibromyoma of the urachus was made.

Urachal cysts and inflammatory conditions arising from the urachus are occasionally met with, as has been emphasized by Dr. Cullen in his book on *The Umbilicus*, but solid tumors of the urachus are truly rare. Up to 1927, when I operated upon this patient, there had been only 20 such cases reported, and 18 of these were malignant. My own and one other case reported by Aveling were the only two urachal fibroids in this series. It is of interest that Aveling showed his specimen in 1886 before the British Gynecological Society and Bland Sutton wrote a description of its microscopical appearance. Additional cases reported in the past eight years have now brought the total number of benign solid tumors of the urachus up to 7, as was shown in a comprehensive article on this subject by Begg.

Fig. 3.—Pyelogram showing the pelvic kidney, which has been converted into a large hydronephrotic sac. The kidney lay entirely below the pelvic brim.

Another case is that of a woman who complained of pain in the left side of the lower abdomen. A tender mass was palpable on pelvic examination and as without an anesthetic the left ovary could not be felt separately from this mass, it was our first impression that we were dealing with a cyst or tumor of the left ovary. But because the catheterized specimen of urine showed some pus we decided to cystoscope the patient before operating upon her. Moreover, the consistency and shape of this mass seemed to me to be different from that of any ovarian neoplasm that I had palpated. Fig. 3, a pyelogram, shows that the tumor in the left side of the pelvis was an ectopic kidney, that lay entirely below the pelvic brim. As it was functionless and heavily infected and the other kidney was normal, a nephrectomy was performed. It is important for the following reasons not to mistake a pelvic kidney for a tumor arising in the peritoneal cavity. First, it is usually possible to remove a pelvic kidney without entering the peritoneal cavity. Second, and this is to be

particularly emphasized, if a surgeon unexpectedly should come upon an infected ectopic kidney when he thought he was operating on an ovarian tumor he would hesitate to remove the kidney no matter in what condition he found it, because without having done a differential phthalein test before operation he could not possibly be sure about the function of the other kidney. Unwittingly he might in such a case remove the better of the patient's two kidneys, or in rare cases her only one.

Soon after seeing this last patient, I examined a four-year-old girl, with a tumor the size of a tennis ball. It could be moved freely around the entire lower abdomen and, having in mind ectopic kidneys, I cystoscoped the child. As she was rather uncooperative, this examination had to be done under an anesthetic. By catheterizing the ureters with opaque catheters, placing the child under a fluoro-

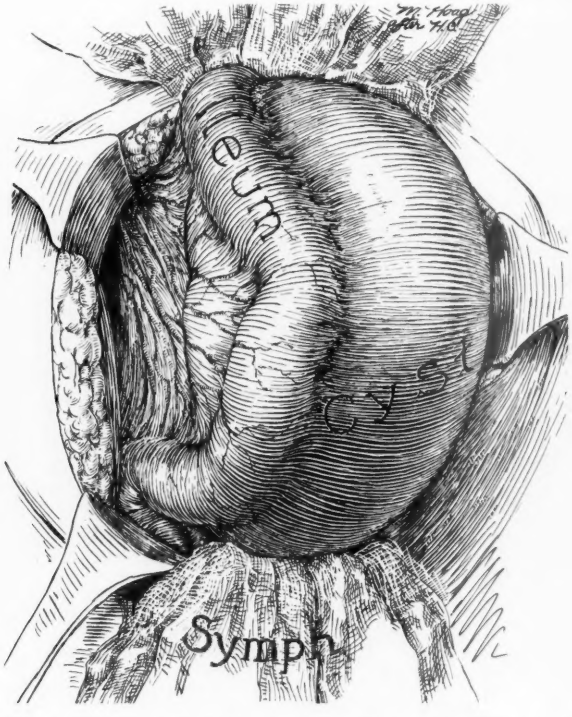

Fig. 4.—Mesenteric cyst in a girl four years of age. It measured 10 by 6 by 6 cm. and was roughly kidney-shaped.

scope and then moving the tumor mass without producing any effect on the visualized ureters, we were able to show that this mass did not arise from the kidneys. Then, thinking that the child probably had an ovarian cyst with a long pedicle, we made an abdominal incision. Fig. 4 shows that this cyst arose in the mesentery. Fortunately, it was possible to remove it without injuring the blood supply of the loop of intestine above it, so that an intestinal resection was not necessary.

This, the last case, demonstrates almost as rare a condition as the fibromyoma of the urachus. The patient, a woman thirty-nine years of age, had a moderate sized myomatous uterus but quite separate from the uterus, kidneys and ovaries, all of which structures could be palpated, was an ovoid mass which was deep in the left side of the lower abdomen. This mass could be moved laterally for a few centimeters but no up and down motion was demonstrated. A diagnosis of retroperitoneal tumor

was made, but we could go no further toward determining preoperatively its nature. At operation we first performed a hysteromyomectomy and then incised the posterior peritoneum. A retroperitoneal cyst lay a little to the left of the midline between the aorta and left ureter and about 3 cm. above the bifurcation of the aorta. In order to rule out an aneurysm, a very small needle was used to aspirate a little of the cyst contents, which to our surprise we found to be milky in character. Without any special difficulty it was found possible to remove this cyst without rupturing it. It measured 10 by 6 by 6 cm. Careful analysis of the cyst contents showed that it contained globules varying in size from 3 to 20 microns, and by using "scarlet red" the presence of large quantities of fat was proved. A diagnosis of retro-

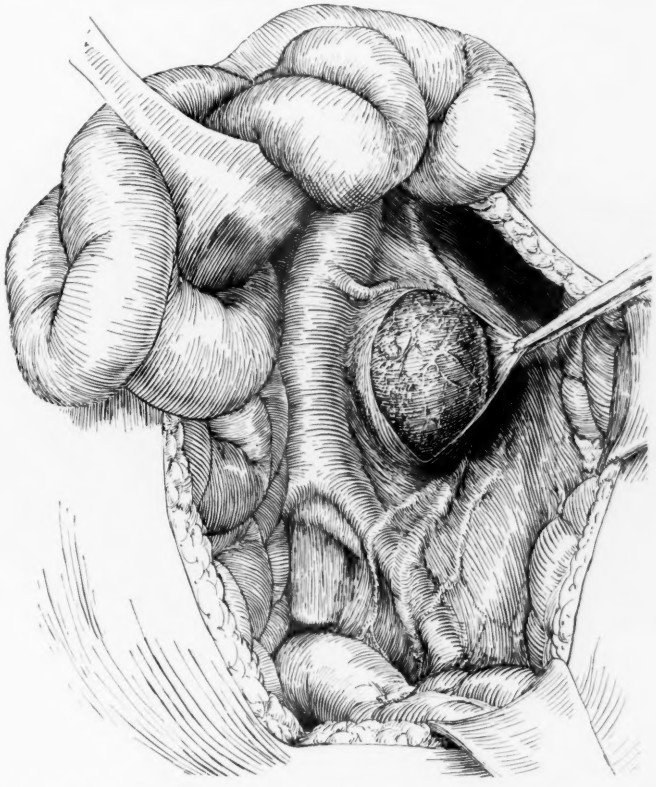

Fig. 5.—A retroperitoneal cyst situated a little to the left of the midline, between the aorta and left ureter and about 3 cm. above the bifurcation of the aorta.

peritoneal chylous cyst was made. Judging from its position, it had probably arisen from the left lumbar lymphatic trunk just before the latter joins the right trunk to form the receptaculum chyli.

In conclusion, I have endeavored, by reporting these unusual conditions, to direct attention to extraperitoneal pelvic lesions and I hope my study of broad ligament abscess has brought out some facts concerning the etiology, diagnosis, and treatment of this condition which may prove of clinical value.

I take this opportunity to thank Dr. Cullen and Dr. Eastman for permitting me to use the records of the Gynecological and Obstetrical Departments in the preparation of this paper.

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DISCUSSION

DR. FREDERICK C. HOLDEN, New York, N. Y.—Dr. Brady has called our attention to the fact that in the Obstetrical and Gynecological Departments at Johns Hopkins Hospital, there were 53 cases of extraperitoneal abscess opened by the abdominal route, and in none of these cases was there a fatality. Patients die either of peritonitis or blood stream infection and the fact that a broad ligament extraperitoneal abscess developed would indicate either a high resistance of the patient or moderately low virulence of the organism.

Contrary to Dr. Brady's experience, of the large number of extraperitoneal infections at Bellevue Hospital, most of them were localized in the retrocervical space, infiltrating the parametrial tissues of the rectovaginal septum. Most of our cases have, therefore, been best drained by posterior colpotomy. Very rarely was the space between the cervix and the bladder involved. Only a small number also localized between the layers of the broad ligament, becoming accessible for operation by the abdominal route. When such localization did occur, we always drained by the method advocated by Cullen many years ago and described by Brady in this paper.

When does Dr. Brady drain? During the stage of indefinite brawny induration or during the stage of definite mass formation which is stony hard in consistency, or does he wait for fluctuation?

When we first used the Elliott treatment at Bellevue Hospital, the patients selected for treatment were those in which we thought the process would go on to abscess formation and the treatment was instituted to hasten fluctuation, but much to our surprise, resolution took place without abscess formation in a number of these patients.

DR. ARTHUR H. CURTIS, Chicago, Ill.—I have become more and more impressed with the relative frequency of adhesions over the anterior surface of the liver in patients who have old gonococcal lesions of the fallopian tubes and, surprising as it may be, we encounter this type of lesion almost *exclusively* in gonococcal infections. I refer to cases free from adhesions elsewhere in the upper abdomen. It would seem natural that anterior liver surface adhesions would occur in postabortive and other infections, but such seems not to be the case.

If we can rule out the more common etiologic factors (such as gonorrheal infection, postabortive and puerperal infection, infections associated with instrumentation, and pelvic tuberculosis), the next most common factor in the causation of chronic pelvic inflammation is the damming back of menstrual fluid and débris by obstructive lesions in the uterus.

In the postabortive and puerperal injection cases I have been greatly impressed with the danger of cervical tears extending into the broad ligament. The only patients I can recall having had a fatal termination after spontaneous full-term labor were three in whom no vaginal examination was made. All three had a spontaneous tear which extended upward into the broad ligament, all developed a blood stream infection, and all died.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I have long been in favor of draining abscesses of the broad ligaments and of the pelvis, but frequently it is difficult to determine when an abscess is to be drained. If drainage is done too early the patient's illness is accentuated and her convalescence delayed. As long as the patient is having chills, and her temperature is making great excursions each day from normal or slightly above to high and back again, it is too early to drain. When, however, the acuteness of the infection has subsided and instead of long excursions the temperature becomes more constant and yet shows no tendency to disappear, then drainage must be considered. One sign is very helpful, when the minimum temperature each day goes higher so that the base line is steplike, pus is under tension and drainage is indicated.

DR. FRED L. ADAIR, CHICAGO, ILL.—In dealing with extraperitoneal lesions, especially in obstetric cases, we should not forget involvement of the veins of the pelvis and the frequency of thrombophlebitis. In my experience I have found it rather difficult to determine that the process is limited and to exclude involvement of the lymphatic vessels and veins.

In my opinion the approach should be through the most obvious channel, that is, where the abscess is pointing, whether through the vagina or through the abdomen. We sometimes find abscesses which have arisen through extension of the process through the ligaments, and the abscess may be found located very high, even in the perinephritic region.

DR. JOHN A. McGLINN, PHILADELPHIA, PA.—My experience at the Philadelphia General Hospital is very much like that of Dr. Holden. The infection of the broad ligaments is one of the most common conditions with which we have to deal. At our hospital the usual etiologic factors of postabortal, postpuerperal and gonorrheal infections are the cause in the vast majority of cases; but in the private cases I should say the most common cause of these abscesses is office cauterization of the cervix.

DR. JAMES C. MASSON, ROCHESTER, MINN.—In considering extraperitoneal tumors of the pelvis, one that has not been mentioned, and which in my experience is not uncommon, is extraperitoneal lipoma. I have seen several such tumors, some of them weighing over 30 pounds. The majority of them start in the kidney region, but occasionally they begin in the fatty tissue in the base of the broad ligament. We should keep in mind these tumors, which can be diagnosed generally by careful clinical examinations and tests. They can easily be removed when small, but it is often difficult to do so when they become large, especially if they extend up into the mesentery of the intestine.

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—My own teachers, Penrose and Baldy, admitted the advisability of opening certain cases above Poupart's ligament, but in actual practice these two men selected few cases which they felt gave the proper indication for this opening. In the majority we waited until the culdesac was definitely involved with swelling and probable fluctuation and opened in that area. I have kept to this practice in my own service.

A supposed pelvic abscess should never be opened without preparation of the abdomen, in order that if a mistake in diagnosis occurs it may be promptly opened.

This I have made an absolute requirement in my service at the Graduate Hospital. I have had two dramatic experiences in which the history, blood examination, and the palpatory findings were those of large pelvic abscesses, and yet on opening the culdesac in both instances we were rewarded, not by pus, but by a tremendous gush of blood. An old, neglected extrauterine pregnancy, resulting in tubal abortion, may give the classical symptoms of pelvic abscess.

DR. BRADY (closing).—In answer to Dr. Holden's question, as to whether or not we wait for fluctuation before operating, I might say that it is our usual procedure to drain extraperitoneally, through the inguinal route, all broad ligament abscesses as soon as a definite mass is palpable above Poupart's ligament. Occasionally no pus is encountered but only a little bloody serum. However, even in these cases the introduction of drains seems to shorten the patient's convalescence.

I agree with Dr. Adair that in broad ligament infections the process is seldom limited to the lymphatics but also involves and extends by the veins. It is of interest in connection with this limitation of some infections to special tissues, to mention again the four cases in which the peritoneal cavity was opened through mistakes in diagnosis. There was no evidence of any peritonitis in any of these cases and still large extraperitoneal broad ligament abscesses were present.

Lipomas of the broad ligament form an interesting group of extraperitoneal conditions, but we have had very little experience with them. In our series we also did not have any instances of perirenal abscess following broad ligament injections, but we did have one patient who developed an ischiorectal abscess two weeks after a broad ligament infection was drained and the same type of streptococcus was cultured from the pus obtained at the two operations.

Of course, the logical way to drain all extraperitoneal abscesses is by the route which leads most directly to the infection, but in our experience, as a general rule, inguinal drainage has yielded us better results than vaginal drainage.

Hunt, Elizabeth: Skin Affections Underlying Pruritus of the Vulva and Anus, Lancet **1**: 592, 1936.

In a study of 300 cases of vulval and anal pruritus seven classifications are made and their respective numbers given:

I.	*General Skin Affections:*		
	Lichen planus	105	
	Seborrheic dermatitis	69	
	Psoriasis	17	
	Eczema	2	
	Leucodermia	4	
II.	*Dermatitis Traumatica et Venenata*	59	
III.	*Local Causes:*		
	Vaginal discharge	3	
	Vaginal prolapse	2	
	Hemorrhoids	2	
IV.	*Parasites:*		
	Scabies	2	
	Ringworm (Dhobie itch)	1	
V.	*General Constitutional Diseases:*		
	Diabetes		12
	Secondary anemia		2
	Disseminated sclerosis		1
VI.	*Psychic*		8
VII.	*Various:*		
	Lichenoid eruption with oral sepsis		2
	Lichenoid eruption with cholecystitis		1
	Lichenoid eruption with malignant neoplasm of liver		1
	Senile pruritus		2
	Imperfect hygiene		2
	Undetermined		3

The author points out the necessity for an accurate diagnosis to prescribe and treat correctly. Particular attention is given to lichen planus and its differentiation from leucoplakia, for in the latter vulvectomy is indicated. Lichen planus should be diagnosed only when there are similar typical lesions at other sites. Seborrheic dermatitis of the genitalia is almost always associated with the disease elsewhere on the body.

H. CLOSE HESSELTINE.

THE RELATION OF THE ENDOCRINE SYSTEM TO TUMOR GROWTH*

The Effect of Hypophysectomy and Pituitary Growth Hormone on Transplantable Rat Sarcoma

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FOR a number of years attempts have been made to link the endocrine system with carcinogenesis and tumor growth. Most of the early studies dealt with the behavior of tumor tissue implanted in close contact with endocrine tissue. The most noteworthy of these was published by Desider Engel, whose observations covered a wide range of endocrines. Engel pointed out that great variations exist in the affinity of hormones for neoplastic tissue. He also pointed out that age, sex, race, and species modify such relations. In his experiments, thymus and thyroid showed inhibitory qualities, the gonadal group had no effect upon tumor growth, and the pituitary gland suggested the presence of a tumor growth accelerating agent. In some later experiments, others showed the tumor inhibiting action of endocrine tissues to be nonspecific and probably not different from the qualities of various somatic tissues.

This particular line of investigation made little progress until the advent of the isolation of specific hormones. Since then, considerable progress has been made and some extremely interesting informations have been obtained. One of the most interesting of these is Lacassagne's study of the relation of estrogenic hormone to carcinogenesis. Lacassagne observed the occurrence of mammary cancer in male mice after the administration of large doses of estrogenic hormone. In this particular strain of mice the females were afflicted with spontaneous cancer of the breast, but the males were rarely victims of this disease. Although the number of animals studied was small, the results are significant as far as selective experimentation is concerned. However, these results do not yet warrant a general application, because they do not prove that estrogenic hormones as a whole can produce mammary cancer under any conditions and in all mammals. The only deduction permissible is that in the particular strain of mice studied by Lacassagne, the mammary cell of the male possesses a tendency

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toward functional mutation of carcinogenic propensity which is dormant in the male but can be awakened by a specific stimulus, such as an estrogenic hormone not ordinarily present. The mammary cell of the female possesses the same carcinogenic propensity in an active state, and since it is constantly exposed to this estrogenic hormone, malignant degeneration is a common occurrence. This subject was discussed again by Loeb in 1935 on the basis of further laboratory evidence. The basic principle underlying this process must be quite similar to that of malignant degeneration following prolonged chronic irritation. Under ordinary circumstances, chronic irritation does not produce cancer. Various other receptive factors must be present before cell mutation reaches a malignant stage. Above all, the cell exposed to irritation must have the faculty of undergoing more than ordinary mutation; the stimulus necessary to set off this process must be specific; and the host must lack resistance to malignant degeneration. This is very well demonstrated in Fibiger's experiments.

Fibiger produced gastric cancer by feeding rats cockroaches infected with certain nematodes. The development of this gastric cancer involved four factors: a specific nematode (spiroptera) had to be present in a specific cockroach (Cuban); the rat fed had to be of a specific species (Norwegian), and then cancer would occur only in a specific organ (the stomach). Even then, not all of the animals would be infected. As soon as the chain of events was broken the results were largely negative.

The more one studies the behavior of cells, the more one is impressed with potentialities of the individuality differentials of cells, so ably described by Leo Loeb. Cells develop a tendency toward functional mutation in changed environments. In other words, the individuality differentials assume injurious faculties in an inadequate environment. The theory of organ and tissue differentials is too complicated to be expounded here. Suffice it to say that the changes of cell characteristics according to this theory are probably largely extrachromosomal phenomena.

There is comparatively little known about the relation between extrachromosomal influences and the incidence of malignancy. That such a relation exists is certain. We call particular attention to Loeb's studies on cell individuality and transplantation of tissues, and to the studies of Little, and Murray and Little, of the existence of extrachromosomal influences on the incidence of mammary tumors in mice. We are convinced from our own tumor studies, which have been carried on for more than eight years and are not yet published, that malignant degeneration is not as simple a process as can be explained on the basis of the Mendelian Law. We agree with Little, and Murray and Little, that the existence of chromosomal influences is of importance in the genesis of neoplasms but that a simple hereditary mechanism is not the sole explanation. It is only natural that in studying extrachromosomal influences cancer research has turned to the hormones. In our opinion, Lacassagne's experiments typify the relation of hormones to tumor growth on this basis.

The entire question of the relation of the endocrine system to tumor growth is exceedingly complicated. Recently Fischer-Wasels evaluated the important contributions in an impartial way. His attitude toward the numerous published suggestions that any hormone may have a direct influence on the origin or growth of malignant tumors, whether in animal or man, is that of disbelief. Fischer-Wasels has repeatedly pointed out that it is not a sudden extraneous factor which changes the normal

into a malignant cell, but that this mechanism is dependent upon a sequence of circumstances ranging over a long period of time. Cells of different tumor constituencies produce different chemical substances and probably are receptive only to a limited number of chemical reactions in the sense of Loeb's theory of cell individuality and characteristics. Probably the same is true of hormonal reactions. Since Otto Warburg demonstrated that the metabolism of the malignant cell differs considerably from that of the normal, it has been suggested that hormones may play a part in bringing about this change in normal cells, with the ultimate result of malignant degeneration. The obvious objection to such speculation is the lack of accurate information concerning the chemical and physiologic individuality of both the normal and the malignant cell.

EXPERIMENTAL STUDIES

Since we have studied tumor growth on the basis of developmental occurrences over a period of years, we could not escape delving into the secrets of the hormonal apparatus. As previously recorded (Emge), we have witnessed the change of transplantable mammary adenofibromas into fibromas and ultimately into sarcomas of a very vicious type. We believe that this alteration has followed the intensification of individuality factors resulting from changes in the biologic surroundings of transplanted tumor materials. In the course of transplantation over many generations, the tumor tissue has been passed through old and young, males and females, castrates of both sexes, and ultimately into highly inbred animals. The result has been sarcoma. At the same time, we have been able to prevent these mutational changes if no new factors were introduced. Thus we still have the original adenofibroma tumor strain and also the fibroma strains developed from it. We have not been able to obtain carcinoma, at least not transplantable carcinoma, by our method, although microscopically a malignant degeneration of the parenchyma is evident in such tumors, which, when again transplanted, produce rapidly growing but cytologically benign adenofibromas that recur after removal but do not metastasize. We are searching for an explanation, and among other studies we have followed the lead of other investigators in studying the relation of the hypophysis to tumor growth.

One of the reasons for the assumption that the hypophysis may bear a relation to tumor growth is based on the finding of cellular changes in the eosinophilic apparatus when tumor growth is present elsewhere in the body.

Such changes were described by Guyer and Claus in rats bearing Flexner-Jobling carcinoma. They were also seen by Wyeth in the hypophyses of carcinoma patients. The reaction expresses itself in vacuolation of the eosinophilic components, similar to castration reactions. But McEuen, Selye, and Thomson hold that this reaction is not specific since it can be produced by other tissues, provided decomposition occurs after implantation. These investigators therefore concluded that the pituitary response ascribed by others to the presence of tumor growth represents only a reaction to chronic absorption of toxic materials.

Another reason for linking the hypophysis with tumor growth is the finding of large amounts of gonadotropic hormone in the urine of certain cancer victims.

This problem was first investigated by Zondek, Zondek and Hartoch, who studied the effect of gonadotropic hormone on the growth of Ehrlich's mouse carcinoma. After failing to influence the growth rate of this carcinoma through the administration of various hormones derived from the thyroid, adrenal, and gonads, these investigators resorted to the administration of large doses of gonadotropic hormone. Various degrees of inhibition and retardation of this neoplasm occurred, but cytologic studies failed to prove that this therapy actually destroyed cancer tissue. It may be concluded, therefore, that while gonadotropic hormone may exert an inhibiting influence on the growth of certain tumors, it does not possess carcinocidal faculties. Cannova repeated these experiments with smaller dosages of the same hormone and obtained similar, but less striking, results. Therefore, it is likely that the tumor growth-retarding action of the gonadotropic hormone is quantitative in nature.

In some of our unpublished studies of the action of gonadotropic anterior pituitary-like and estrogenic hormones on the growth rate of benign tumors in young rats, we have observed that when the dosage of this hormone is increased sufficiently to disturb the normal state of health, tumor growth is retarded in a way similar to that caused by chronic disease, starvation, or cachexia. Consequently we have serious doubt that the action of any hormone as a general tumor-inhibiting agent is specific in a broad sense.

This is borne out to some degree by Saphir's studies on the increase of gonadotropic hormone in the urine of patients afflicted with genital and extragenital malignancies. It was only in the genital that Saphir found striking increases of gonadotropic hormone. The gonadotropic reaction observed by Zondek and others, therefore, may have to be interpreted as being specific only for tumors of genital origin. This reaction probably represents an intensification of pituitary response to an increased output of gonadal hormone when the mass of certain cells of genital origin is markedly increased. It is therefore of considerable interest that Paul Engel and Tanzer, who repeated the experiments of Zondek and others with different tumors such as various transplantable mouse sarcomas, found that the growth of these tumors either could not be, or was only slightly, retarded. Recently Ludwig and v. Ries thought the mice of their colony were refractory to the inoculation of an unspecified cancer emulsion when previously treated with prolan. All of these observations are very interesting and important, but they demand broader applications in tumor experimentation before they can be accepted as facts applicable to the principles of tumor growth in general.

A third reason for linking the pituitary gland with tumor growth is based on the supposition that the growth hormone may play an important part in tumor development. The study of this problem presents considerable technical difficulty because it requires the destruction of the hypophysis, with a resultant high mortality of experimental animals. It also introduces various new factors which are not present under normal conditions, as exemplified by the marked depression of metabolism in general and the complete alteration of hormonal rela-

tions. The other endocrine glands very rapidly undergo atrophy after pituitary ablation. Hence, hypophysectomy eliminates not only pituitary factors but it also decreases other endocrine secretions which may bear directly on the physiology of certain neoplasms.

The effect of hypophysectomy on tumor growth has been studied by Hayashi, Bischoff and others, McEuen and others, Ball and Samuels, and Franseen and McTiernan. With the exception of Hayashi, who studied rabbit sarcoma, these investigators used either Walker rat carcinoma 256, rat sarcoma R-10, or mouse sarcoma 180. Bischoff, Maxwell, and Ullmann also studied spontaneous mouse mammary carcinoma. Hypophysectomy in mice is very difficult and the results are rather discouraging. The investigators last mentioned therefore resorted to heavy irradiation to the pituitary region either by x-ray or by radon-seed implantation, using the decrease of body weight as the standard for the effectiveness of this method.

We shall not enter into the controversy as to the efficacy of destroying pituitary function by irradiation versus hypophysectomy, but shall content ourselves with a brief review of the end-results reported by the various groups of workers. It may be stated in a general way that all investigators agree that hypophysectomy in rats or the destruction of pituitary function by irradiation in mice leads to a retardation of tumor growth similar to that seen in prolonged starvation, but to a slightly greater degree. There are differences in response in different types of tumors.

McEuen and Thomson contend that the retardation of growth in hypophysectomized animals is probably independent of the pituitary growth hormone but constitutes a part of a general decrease in somatic response after hypophysectomy. These workers believe that their studies tend to discount the importance of the anterior pituitary hormone, particularly the growth hormone, in tumor growth. This opinion is not shared by Ball and Samuels, nor by Bischoff and his coworkers. Franseen and McTiernan very recently reported experiments in which hypophysectomy showed little or no retarding influence in Walker carcinoma 256.

In the following paragraphs we submit the results of our own observations on the relation of the growth hormone to the growth of the autogenous mammary rat sarcoma developed by us and designated hereafter as rat sarcoma E (Emge), the particular strain being designated by numbers. The cellular composition of these strains varies from a highly mature spindle-cell sarcoma to a fairly immature mixed-cell type. In the following experiments, strains E-2 and E-5 were studied. Both strains produce rapidly growing tumors which ordinarily kill in from three to four weeks if not removed. They do not metastasize, but recur rapidly after removal. Transplantation yields 100 per cent "takes." The growth rate of these tumors is uniform and conforms to the basic laws of tissue growth, always showing a slight retardation in the volume curves with increasing size, as described by us in our studies of tumor growth in pregnancy (Emge).

The growth rate in comparison with that of the body of the host is positively heterogonic,* i.e., the tumor growth rate far exceeds that of the body of the host. Since the tumor does not metastasize and grows well in the groin of the host, observations and measurements can be made with reasonable accuracy. The strain of rats studied is a Wistar Institute derivative, bred pure at our institution for some thirty years.

Each experiment was started with a much larger number of hypophysectomized rats than shown in the accompanying charts. The very high mortality reduced the number of completed observations to a few. For the sake of uniformity we preferred to eliminate incomplete observations and report only on tumors which grew for a sufficiently long period. The total number of animals studied is 74. This number is rather small, and requires a continuation of the study before final conclusions can be offered.

In order to save space, all observations are recorded in graphic form. Body weights are charted in the conventional way. Tumor volumes, estimated according to the prolate-spheroid formula ($4/3\pi ab^2$), are recorded on logarithmic paper, and the curves therefore appear steeper than when charted in the conventional manner.

EXPERIMENT 1

Donor L-1021, female, Sarcoma E-2, 13 animals (Fig. 1). Ten of the animals studied were approximately seventy-three days of age and 3 were one hundred and forty days old at the time of tumor implantation. As indicated in the charts, the majority of the animals were males. In the hypophysectomized group, animal "A" was found to have been only partially hypophysectomized. Groups 2 and 4 were injected with 1 c.c. of a growth hormone prepared by us according to the Evans formula. Injections were given subcutaneously, beginning with the day of implantation and continuing daily for the duration of the experiment. This growth hormone was not standardized and therefore the actual amount given was not known except for quantity. However, it was found to be very active. It probably contained traces of gonadotropic hormone, since we found macroscopic changes in the ovaries. All animals were hypophysectomized at the time of implantation.

A comparison of the body weight curves of the four groups (see Chart 1) shows that the body weight of the hypophysectomized animals failed to rise at the rate observed in Groups 1 and 2. The partially hypophysectomized animal "A" in Group 3 showed a mild rise, but considerably below the expected increase for the normal. The older animals "A" in both Groups 1 and 2 did not show the marked rise in body weight that occurred in the younger animals. The behavior of the body weight of animal "B" in Group 4 is unusual and probably signifies a greater receptiveness to the administration of the hormone. Comparing Groups 1 and 2, it is evident that the majority of the animals given hormone gained more rapidly

*Julian Huxley, in *Problems in Relative Growth*, styles an organ growing at the same rate as the body, as *isogonic*, and at a different rate as *heterogonic*, as originally suggested by Pèzard in 1918. *Positively heterogonic* means an increase in relative size as related to growth. *Negatively heterogonic* means a decrease in relative size but an increase in absolute size.

than the controls, and a comparison of these two groups with Group 3 shows that hypophysectomy distinctly interfered with an increase in body weight. The response in Group 4 was controversial and inconclusive.

On Chart 2 are the logarithmic growth curves of tumor volumes recorded as successive prolate-spheroids. A comparison of the four groups shows only minor

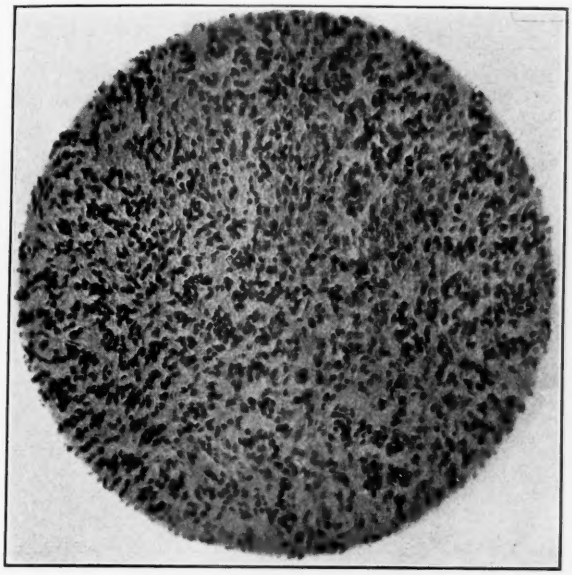

Fig. 1.—Experiment 1. Donor L-1021, female, Sarcoma E-2.

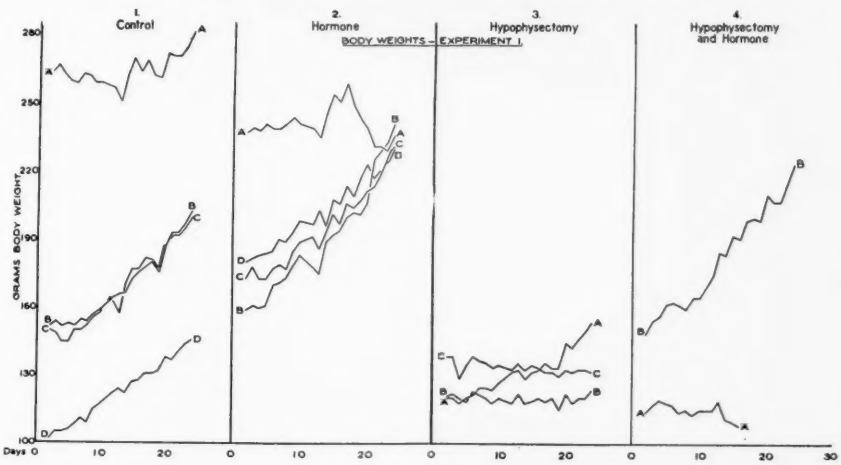

Chart 1.—Experiment 1. Body weight chart. Donor L-1021 ♀. Sarcoma E-2. Animal age: 10 animals approximately 73 days, 3 animals 140 days. Sex: Males (♂) and females (♀) as indicated in tumor volume chart. Hypophysectomy: At time of implantation. Total ablation of pituitary in all except A of Group 3. Hormone: 1 c.c. Evans' alkaline extract subcutaneously daily from time of tumor implantation. Days: Time from tumor implantation to removal.

differences between the ultimate volumes reached. There is a greater variability with a slight increase in tumor volume in Group 2 and a slight decrease in Group 3. In

Group 4, animal "A" died prior to the ultimate time for observation, but judging from the volume reached by the time of death, this tumor probably would have been equal in volume to "B." In general, the differences in ultimate volume between the four groups are not great, and when compared with the body weight curves it is apparent that there is a similar, but more marked, variation. In Group 2, animal "A" showed the same drop in body weight as it showed in tumor volume. In Group 3, animal "A," which was only partially hypophysectomized, showed also a greater body weight and tumor volume than "B" and "C." In Group 4, the marked increase in body weight is not explainable on the basis of unusual increase in tumor volume, since this tumor did not reach an unusual size as compared with controls.

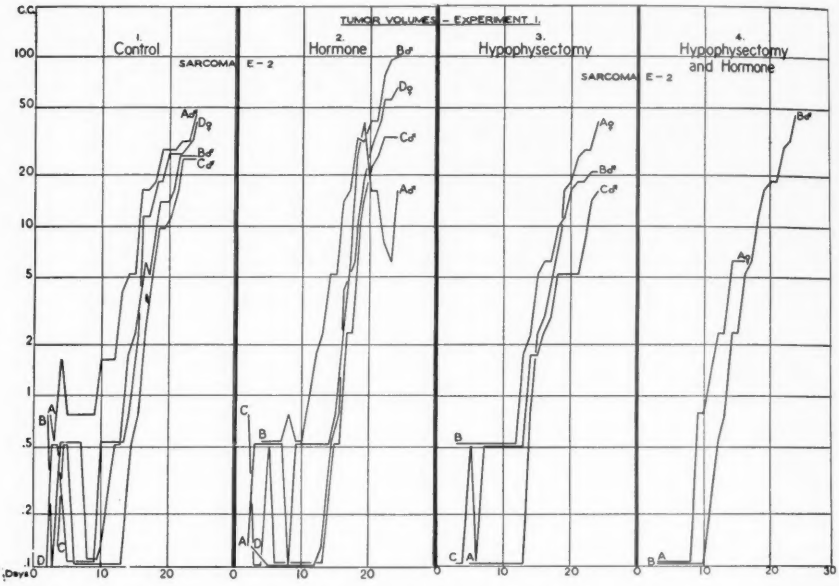

Chart 2.—Experiment 1. Tumor volume chart. Donor L-1021 ♀, Sarcoma E-2. c.c. Tumor volume (according to prolate-spheroid formula). Days: Time from tumor implantation to removal. (See body weight chart of Experiment 1.)

EXPERIMENT 2

Donor L-1111, male, Sarcoma E-5, 20 animals (Fig. 2). Sixty-day-old male animals were studied. Hypophysectomy and tumor implantation were carried out at the same time. The growth hormone used in Experiments 2, 3, and 4 was Antuitrin-Growth, prepared and standardized by Parke, Davis and Company. In this experiment, 0.5 c.c. (5 R.U.) of growth hormone was injected intraperitoneally daily, beginning three days after tumor implantation. All recordings on Charts 3 and 4 were made according to the methods described in Experiment 1.

The behavior of the body weight curves, with the exception of Group 2, is quite similar to that of Experiment 1. There are certain variations, such as animal "C" of Group 1, which showed an unusual increase in body weight, probably due to the rapid growth of the tumor (see Chart 3). The similarity in body weight gain of Groups 1 and 2 is evident. The behavior of the body weight curves of the animals of Groups 3 and 4 conforms to that expected in hypophysectomized animals with or without replacement therapy. A comparison of the volume curves, on the other hand, shows again that variations occur in each group. In the control group, tumor volume showed a greater variation than expected, probably due to extensive abscess

formation and surface erosion of the tumor in animal "A," and to some degree in animal "D." In the hypophysectomized group, tumor volume was generally below that of Groups 1 and 2, but the decrease did not parallel the marked decrease in

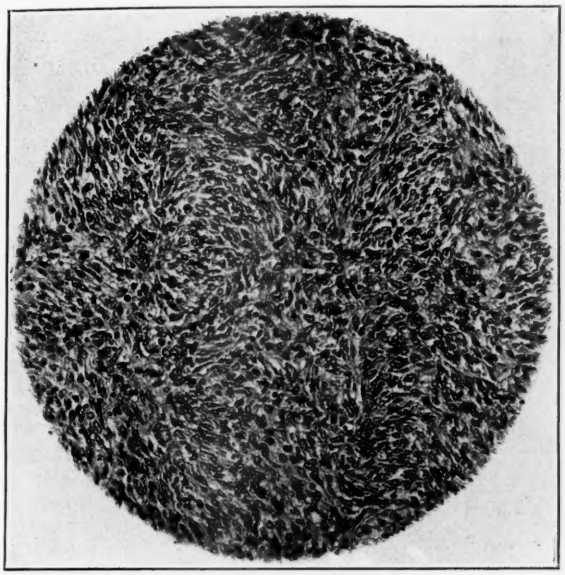

Fig. 2.—Experiment 2. Donor L-1111, male, Sarcoma E-5.

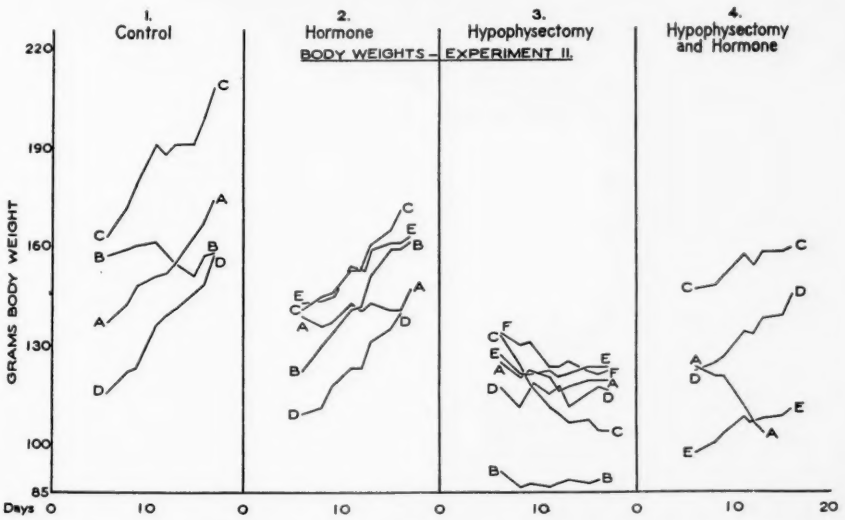

Chart 3.—Experiment 2. Body weight chart. Donor L-1111 ♂, Sarcoma E-5. Animal age: 60 days. Sex: Males. Hypophysectomy: At time of tumor implantation. All animals completely hypophysectomized. Hormone: Antuitrin growth (Parke, Davis & Co.). 0.5 c.c. (5 R.U.) intraperitoneally daily beginning three days after tumor implantation. Days: Time from tumor implantation to removal.

body weight. The small dose of hormone given in Group 4 was sufficiently potent to allow the animals a constant but retarded weight gain, except animal "A," which was unaffected.

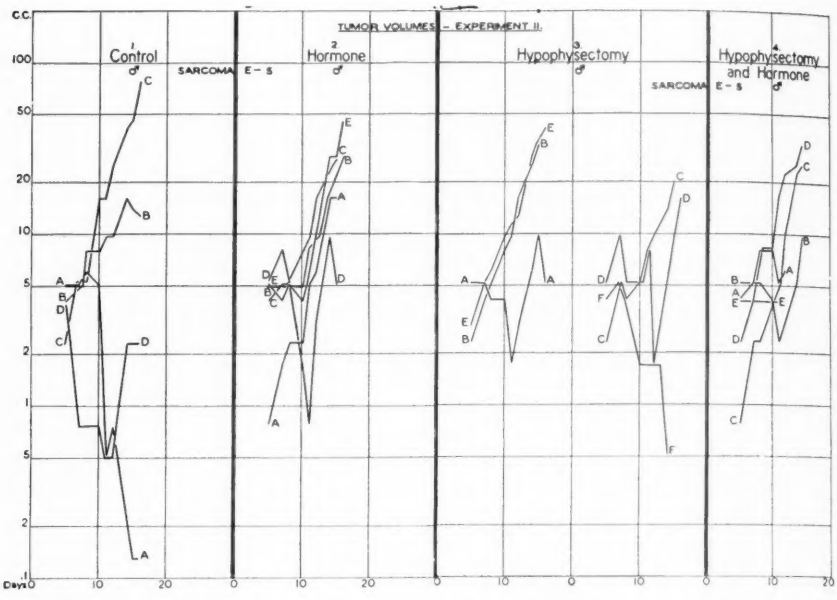

Chart 4.—Experiment 2. Tumor volume chart. Donor L-1111 ♂, Sarcoma E-5. c.c. Tumor volume (according to prolate-spheroid formula). Days: Time from tumor implantation to removal. (See body weight chart of Experiment 2.)

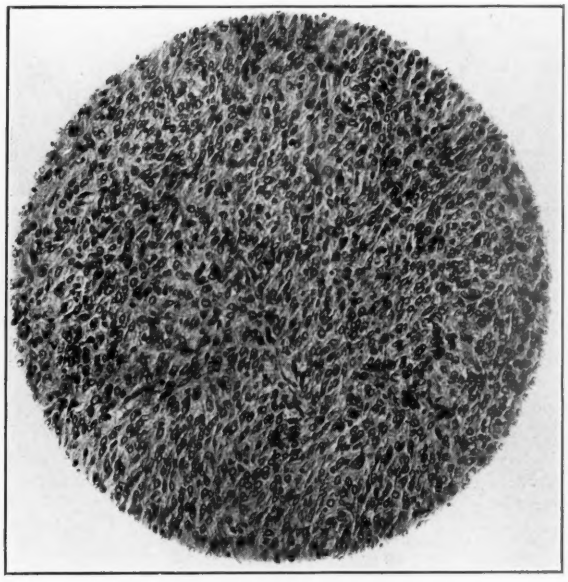

Fig. 3.—Experiment 3. Donor L-1164, male, Sarcoma E-5.

EXPERIMENT 3

Donor L-1164, male, Sarcoma E-5, 18 animals (Fig. 3). All animals studied were males fifty-seven to sixty-one days old. Hypophysectomy was done from one to three days after implantation of the tumor. In Groups 2 and 4, 1 c.c. (10 R.U.) of growth

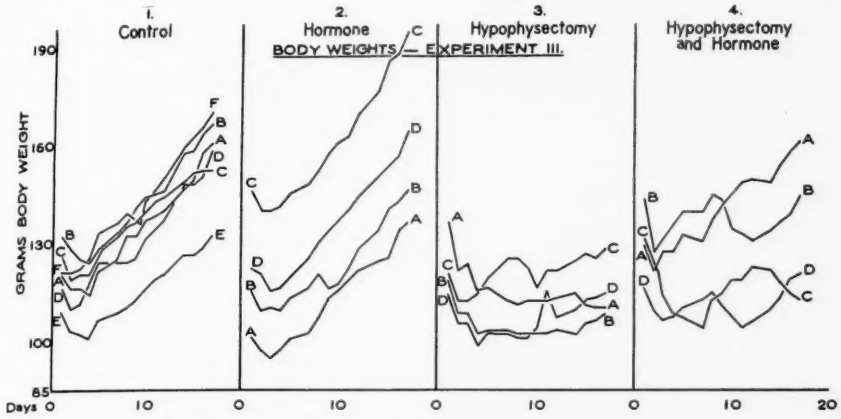

Chart 5.—Experiment 3. Body weight chart. Donor L-1164 ♂, Sarcoma E-5. Animal age: 57 to 61 days. Sex: Males. Hypophysectomy: One to three days after tumor implantation. All animals were completely hypophysectomized. Hormone: Antuitrin growth (Parke, Davis & Co.). 1 c.c. (10 R.U.) intraperitoneally daily from time of tumor implantation. Days: Time from tumor implantation to removal.

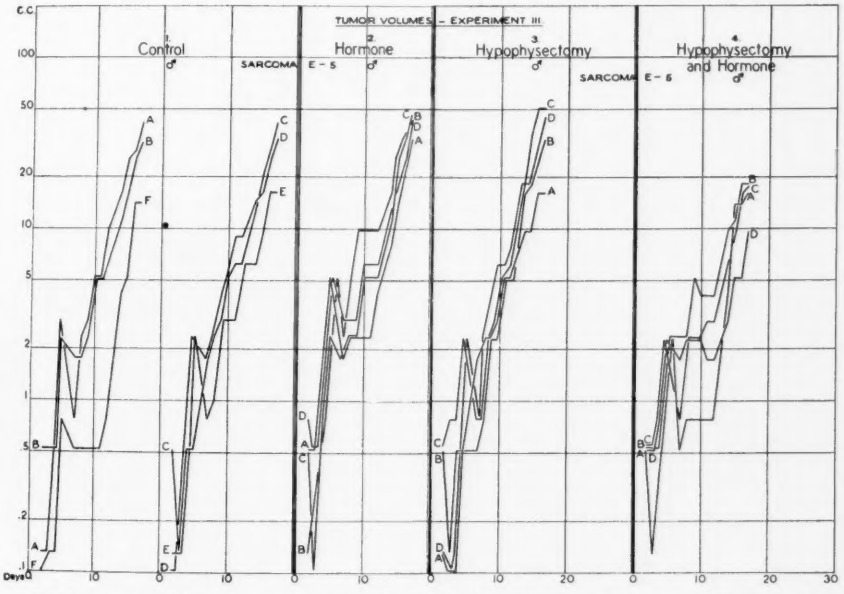

Chart 6.—Experiment 3. Tumor volume chart. Donor L-1164 ♂, Sarcoma E-5. c.c. Tumor volume (according to prolate-spheroid formula). Days: Time from tumor implantation to removal. (See body weight chart of Experiment 3.)

hormone was injected intraperitoneally daily from the time of implantation. A comparison of the body weight curves on Chart 5 shows the general differences discussed in the previous experiments. The response of the hypophysectomized animals to the hormone is again evident. A comparative study of the tumor volume

curves on Chart 6 shows less difference between Groups 1, 2, and 3 than in the previous experiments. There also is a greater uniformity of tumor volume in general. It is apparent that the nonhypophysectomized animals receiving growth hormone did not grow larger tumors than the controls. Tumor volume in the hypophysectomized animals was about as great as in Groups 1 and 2, while in Group 4 it was definitely below that of the other three groups. The behavior of the tumor in Group 4 was unusual, particularly since the body weight curves of the hosts increased as expected. Therefore, the tumor growth is negatively heterogonic; i.e., the volume curve of the tumor is below that of the control when tumor volume and body weight are compared.

EXPERIMENT 4

Donor 32614, male, Sarcoma E-2, 24 animals (Fig. 4). All animals studied were males sixty-one to sixty-eight days old. Of the original 25 animals hypophysectomized, 7 lived long enough to be included in this experiment. In both Groups 3

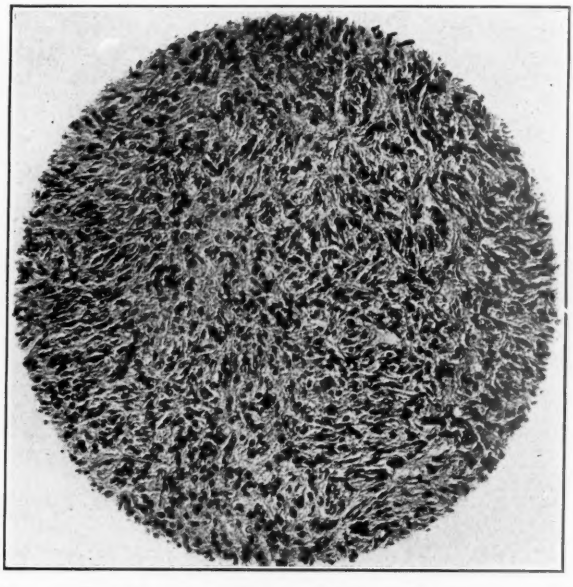

Fig. 4.—Experiment 4. Donor 32614, male, Sarcoma E-2.

and 4, partial hypophysectomies occurred. Implantation of tumor tissue was postponed for two weeks after hypophysectomy. All animals were implanted on the same day. A group of the controls, as well as of the hypophysectomized, were given daily intraperitoneal injections of 2 c.c. (20 R.U.) of growth hormone. Injections were begun on the day of implantation. The high mortality among the hypophysectomized animals, and particularly among those receiving hormone, precluded our obtaining sufficiently long observations to be recorded here. All animals, with one exception, were sacrificed 14 days after implantation. Chart 7 graphically demonstrates the increase in body weight and definitely shows that the rate of weight increase in Groups 1 and 2 is about equal. Growth hormone failed to increase body weight. In the hypophysectomized group, it was demonstrated that complete hypophysectomy prevented weight increase. The presence of a very small fragment of pituitary gland, on the other hand, as demonstrated in animal "D" of this group, permitted a normal weight increase for three weeks, when a slight loss of weight was noted. The same may be seen in Group 4, in which hypophysectomized animals received hormone. The partially hypophysectomized animals "A" and "C" increased

in weight normally. The one animal which was completely hypophysectomized continued to lose weight in spite of the fairly large dose of growth hormone administered. It may be seen in all groups that the implantation of the tumor interfered very little with the expected weight behavior. The continued drop in weight of

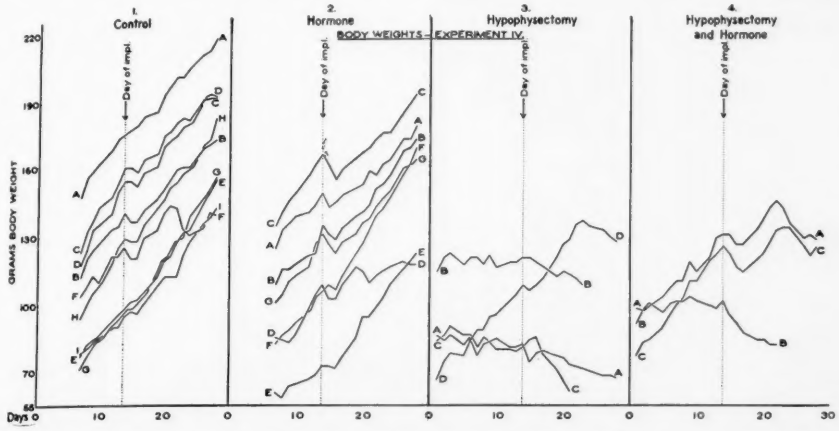

Chart 7.—Experiment 4. Body weight chart. Donor 32614 ♂, Sarcoma E-2. Animal age: 61 to 68 days. Sex: Males. Hypophysectomy: Two weeks prior to implantation. In Group 3, Animal D and in Group 4, Animals A and C are partially hypophysectomized. Hormone: Antuitrin growth (Parke, Davis & Co.). 2 c.c. (20 R.U.) intraperitoneally daily from time of tumor implantation. Days: Time from observation (approximately two weeks before tumor implantation) to tumor removal. Day of implantation indicated.

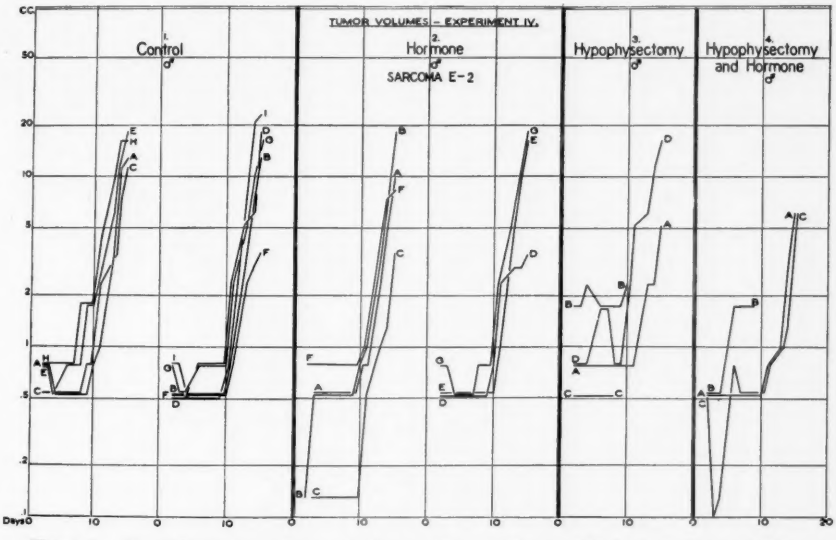

Chart 8.—Experiment 4. Tumor volume chart. Donor 32614 ♂, Sarcoma E-2. c.c. Tumor volume (according to prolate-spheroid formula). Days: Time from tumor implantation to removal. (See body weight chart of Experiment 4.)

animals "A" and "C" of Group 3 and "B" of Group 4 is not attributable to the growth of the tumors, since these particular tumors were exceedingly small at the time of removal.

On Chart 8 the tumor volume for each group is recorded in graphic form. The control and hormone groups produced tumors of approximately the same volume.

The completely hypophysectomized animals of Group 3 grew either insignificant or very small tumors. The partially hypophysectomized animal "D" conformed more closely to the controls. In Group 4, the completely hypophysectomized animals receiving growth hormone also grew insignificant or very small tumors, and the two partially hypophysectomized animals grew tumors less voluminous than the average control group. We may say, therefore, that in this experiment growth hormone did not increase the growth of the tumor, but that hypophysectomy inhibited the growth beyond that expressed by the progressive loss in body weight.

DISCUSSION

Notwithstanding the limited number of observations, our results were sufficiently uniform to permit certain deductions.

All of our tumor material was studied microscopically. In no instance did hypophysectomy or substitution therapy alter the cellular appearance or constituency.

With few exceptions, the comparative body weight changes of each group were practically the same. Growth hormone accelerated the weight increase of the control animals only very slightly or not at all. Complete hypophysectomy invariably arrested and decreased body weight. Only a few of the hypophysectomized animals increased in weight when given growth hormone, but the increase, with one exception, did not parallel that of the controls.

Variations in tumor volume occurred in each group studied. The very marked retardation of tumor growth in the hypophysectomized group in the last experiment is more striking than in the other three, and probably is due to the longer interval between hypophysectomy and implantation. It is interesting that distinct differences in growth behavior occurred in the two derivatives of Sarcoma E-5. These differences were not as markedly present in the Sarcoma E-2 derivatives. However, allowing for some unusual variations in Tumor E-5 in Experiment 2, the general growth potentialities were the same in all groups of all experiments. Only in Experiment 1, where a crude growth hormone extract of undetermined potency was used, a slight increase in volume gain over the control group occurred. It is more than likely that this hormone extract contained other pituitary factors, as pointed out in Experiment 1. This may explain the difference in tumor behavior in this group, because in all other experiments growth hormone substitution was not sufficient to overcome the deficiency set up by pituitary ablation, regardless of the dosage given. It was interesting, also, to note that hypophysectomy can affect tumor strains differently although they may be as intimately related as E-2 and E-5, which were derived from the same stem. Thus, in Experiment 2 the retardation of growth was far more apparent than in Experiment 3. In fact, in Experiment 3 the tumor volume of the hypophysectomized group nearly paralleled that of the controls, both treated and untreated. The same was true of Sarcoma E-5 in Experiment 1. On the other hand, in Experiments 2 and 4, Sarcomas E-5 and E-2 both

showed definite retardation of tumor growth. This suggested to us that even in tumors of the same cellular constitution and of common origin, the behavior of the individual derivatives may materially differ under identical conditions because of unknown changes in extrachromosomal influences.

We were surprised by the unusual behavior of the tumor implanted into hypophysectomized rats treated with growth hormone. We found that even fairly large doses failed to bring the tumor growth to normal, and in some instances it even dropped below that of the untreated animals. It may be reasonable to presume that the larger dosage of hormone exerted a toxic effect upon the tumor, although we could not prove this to our satisfaction by the microscopic studies. We are therefore at a loss for an explanation of this occurrence.

We may safely say that as far as the behavior of our tumors was concerned, the tumor volume paralleled that of the body weight increase except in a number of hypophysectomized animals. Here the tumor volume behaved erratically, showing definite retardation in some instances, and none in others. It is also interesting that tumors showing retardation did so to a lesser degree than was expected from the behavior of body weight.

That tumor growth was retarded but not arrested in hypophysectomized animals, and that tumor growth progressed out of proportion to the loss of body weight of the host are shown in Table I. This was true of both strains of sarcoma, although there were again evident differences between E-2 and E-5. We realize that the figures for hypophysectomized animals implanted with Sarcoma E-2 allow a wide margin for error, for it is quite probable that with a larger series the figure for daily tumor weight gain would have been greater but probably still below that of normal animals, as in E-5, shown on the same chart. Nevertheless, the fact remains that the hypophysectomized animals not only lost weight ordinarily, but they also grew less tumor than the controls, although marked variations of growth behavior occurred.

We believe that our transplantable sarcoma is dependent only to a limited degree upon the hypophysis. We believe, also, that its growth is not increased by the administration of growth hormone, and that, even after discontinuance of pituitary secretion, the tumor may follow inherent growth propensities but may be impeded by an altered metabolism.

We are in agreement with McEuen and his coworkers, and others, that hypophysectomy retards, and at times arrests, tumor growth, depending to some extent upon the time relation between hypophysectomy and tumor implantation. Judging solely from our own experience, we have no reason to believe that malignant cells are necessarily more sensitive to pituitary influences, as suggested by Ball and Samuels,

although in their experiments an autogenous fibrosarcoma and a Walker carcinosarcoma showed striking retardation in hypophysectomized animals. It will be necessary to study the behavior of many different tumors and tumor strains before this statement can be accepted as applicable to all malignant cells. On the other hand, our experiments bear out their belief that under normal conditions available pituitary secretion is at a maximum and that the addition of growth hormone will not increase the inherent growth rate of tumors.

TABLE I. DAILY TUMOR AND BODY WEIGHT CHANGES OF 60-DAY MALE RATS*

CONTROL SERIES			HYPOPHYSECTOMIZED SERIES		
ANIMAL NO.	DAILY TUMOR WEIGHT GAIN GM.	DAILY BODY WEIGHT CHANGE GM.	ANIMAL NO.	DAILY TUMOR WEIGHT GAIN GM.	DAILY BODY WEIGHT CHANGE GM.
Implanted With Sarcoma E-2					
1220	0.634	+2.34	1213	0.708	+1.30
1221	0.591	+2.17	1218	0.304	−0.30
33178	0.586	+3.07	33182	0.157	−1.07
33184	0.451	+2.28	33193	0.074	−1.33
33196	0.473	+2.10	33206	0.050	−2.85
33217	0.642	+2.64			
33220	0.732	+4.00			
33233	0.175	+1.00			
33245	0.677	+4.07			
33271	0.650	+3.78			
33275	0.895	+3.35			
Group Av.	0.591	+2.80	Group Av.	0.258	−0.85
Implanted With Sarcoma E-5					
32101	0.012	+2.31	32102	1.066	−0.02
32116	2.000	+2.81	32104	0.714	−1.81
32136	0.058	+2.62	32114	0.256	−0.06
32432	1.411	+2.50	32137	1.019	−0.25
32434	0.658	+2.12	32141	0.025	−0.62
32452	1.578	+1.62	32099	0.228	−0.37
32467	0.507	+1.43	32448	0.312	−1.62
32455	1.062	+2.62	32454	1.000	−0.62
32496	0.480	+3.06	32458	1.462	+0.31
			32466	1.062	0.00
Group Av.	0.862	+2.35	Group Av.	0.714	−0.51

*Animals of Experiments 1 and 4 implanted with Sarcoma E-2. Animals of Experiments 2 and 3 implanted with Sarcoma E-5.

The interesting work of Bischoff and his coworkers, showing that severe irradiation of the hypophysis will retard tumor growth to the same extent as hypophysectomy, has not yet been repeated by us. Their observation that growth retardation can be offset to some degree by growth hormone substitution was observed by us only in a few instances.

We agree with McEuen and others, and Franseen and McTiernan, that there exists a relation between the pituitary gland and tumor growth, but we believe that it does not materially differ from the somatic response of the tumor host.

CONCLUSIONS

1. Allowing for known variations, the administration of growth hormone did not increase the growth propensities of our autogenous rat Sarcomas E-2 and E-5.

2. Growth hormone administered to hypophysectomized rats failed, in most instances, to stimulate tumor growth to the normal rate.

3. Complete hypophysectomy affected the growth of our tumors variably. In most cases, growth continued normally. Retardation was slight, and complete arrest only rare. The greatest retardation occurred when the interval between hypophysectomy and tumor implantation was lengthened.

4. Hypophysectomy or the administration of growth hormone failed to change the cytologic appearance of the tumors studied.

We gratefully acknowledge the services of Dr. P. E. Hoffmann, who performed all of the hypophysectomies for this study.

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DISCUSSION

DR. SAMUEL H. GEIST, New York, N. Y.—It is apparent from the presentation of Dr. Emge's paper that the question of the relation of hormones to tumor growth is a complex one. Two aspects of the problem immediately present themselves. One is the effect that must be exerted on normal quiescent cells to change them into abnormal ones. The second is the effect on such cells to increase their growth rate. These are two entirely separate problems.

Hofbauer had the idea that the pituitary hormone was involved in the first of the two actions, and to support his contention transplanted the eosinophilic portion of the

pituitary to animals and observed changes in the cervix that he thought were suggestive of neoplasm. We are not at all convinced that they represent neoplastic changes.

It is known that certain substances called carcinogenic can stimulate tissues to such an extent that typical tumor growth will result. Such experiments were done on rabbits using a tar preparation as the carcinogenic agent. The tar preparations, clinically, seemed to be very closely related to estrogenic substances. Engel was successful in producing lesions in the cervix that resembled early carcinoma by injecting monkeys with estrogenic substances, but in his cases the cervix had previously been traumatized. Apparently there was more than one factor responsible.

Second, as to the growth-stimulating factor, it does not seem that the hormone itself can be entirely responsible. In gigantism while there is an excessive rate growth there is nothing suggesting malignancy. The same thing is true if one gives to an immature animal growth hormone. The animal grows rapidly but does not develop a malignant tumor. If the hormone is concerned with malignancy, there is some other factor that sensitizes the cells to respond. Some men have found that by hypophysectomizing animals the growth is retarded and if the hormone is given, contrary to the results that Dr. Emge obtained, the growth is again stimulated to develop.

I have had occasion to examine 250 pituitaries from a large group of patients who had died from various causes. My interest was centered more in the morphologic changes that occurred in the various ages and sexes. Among the 250 there were 37 glands obtained from patients who had died of carcinoma of various types. Histologic study failed to show any changes in the eosinophilic portion that could not be accounted for by the variation in age or sex. Of course, one could immediately say that it is perfectly possible for a cell to have a functional disturbance without recording it in a morphologic change.

Hofbauer made the suggestion that, because of the effect that the growth hormone had on tumors, by decreasing the pituitary activity one might get better results than by simple operation alone. Recently several papers have appeared from German clinics in which the authors stated that the results obtained in carcinoma of the uterus are somewhat better if a combination of pituitary x-ray and surgery is employed than by surgery alone. That, of course, remains for the future to prove.

Sarcoma is apparently not so susceptible to the effects of the growth hormone, and likewise transplanted tumors do not show the same response as do spontaneous tumors.

Dr. Emge's results seem to indicate that there is no relation between growth hormone and malignant changes. Of course, the problem being so difficult, it is unfair to conclude that there is no relation. Such experiments as Dr. Emge's should be persisted in.

DR. EMIL NOVAK, BALTIMORE, MD.—There is at present much interest in the question of the possible relation of hormones to tumor growth, and especially of the estrogenic substances to cancer. There has always been a rather deep-seated, almost traditional feeling that tumors are in some way brought about by a disturbance of growth phenomena. The older concept was that a tumor consists of cells in which growth propensities have got the upper hand, while other cell functions have retrogressed. As regards cancer, the further generalization was drawn that the growth balance between the different types of tissue was disturbed, so that, for example, an abnormally growing epithelium could melt down the normal barriers between epithelium and connective tissue and thus assume invasive characteristics. Vague and speculative as these hypotheses were, they lend added interest to Dr. Emge's work, in which an attempt is made to throw light on the influence of the growth hormone

upon tumor growth. His results, as you have heard, have been in the main quite negative.

As regards Dr. Emge's method of attacking the problem, two comments suggest themselves to me. The hormone preparations with which he worked contain not only the growth hormone, but also at least small amounts of the sex hormone, and at least traces of protein. Since in spite of this, the preparations produce definite growth changes in laboratory animals, and since Emge's results on tumor growth were so unimpressive, this objection does not vitiate his results.

More important, perhaps, is the fact that he used hypophysectomized animals for his study. When hypophysectomy is done, one removes not only the growth principle but many others of profound importance to the body, such as the thyrotropic and adrenotropic principles, the sex hormones, and several others, and this must produce a profound effect upon the nutritional functions, an effect perhaps comparable to that seen in cachexia hypophyseopriva or Simmond's disease, in which the constitutional depravity is so extreme that death almost always ensues. Quite a number of Dr. Emge's hypophysectomized animals died, as he has said, and in those which did not it would seem that the nutritional upset would blur and confuse the interpretation of results. Only the growth hormone, presumably, was put back into the animals' circulation whereas a number of vital principles had been removed by the hypophysectomy.

For this reason, it would seem to me that other methods of study of this problem, such as the investigation of the effects of various hormones upon tissue cultures of tumor cells, might be more productive of definable results.

DR. EMGE (closing).—No doubt there remains much more to be said which must wait until our investigation has progressed sufficiently to permit broader deductions. At this moment our results must be interpreted within the strictest confine of this highly specialized field of investigation.

I fully realize that this sort of research is looked upon by many as of no particular value because results are not at once applicable to clinical medicine. Yet more information gathered in this fashion may ultimately yield information highly acceptable to the clinician. Our ultimate hope is to shed some light upon the question whether or not there is a relation between tumor growth and the endocrine system. It will answer a very important question and that is, are we safe in administering large doses of hormonal substances over long periods of time without awakening dormant carcinomorphic elements?

Clauberg, C.: Unusual Gynecologic Findings in Children, Deutsche med. Wchnschr. **61:** 1668, 1935.

Occasionally a malignant tumor or a foreign body furnish the cause for a persistent vaginal discharge in a child, as for instance, in the case of a four-year-old girl who rapidly succumbed to a malignant angioendothelioma of the vagina in spite of radium treatment.

Foreign bodies were detected in two other cases: A girl of six masturbated with a slate pencil, and in a girl of eight, small pebbles and two safety pins, one of which was opened, stayed in the vagina for over a year. The hymenal opening was very small and prevented a thorough examination. A surprisingly good view could be obtained through a small cystoscope after ballooning the vagina with water.

A case of severe impaling injury is also reported where the complete transverse separation of vagina and urethra could be detected only after an extensive Schuchardt-Duehrssen incision; while vulva and hymen showed nothing but contusions.

G. E. GRUENFELD.

ESTROGENIC SUBSTANCES IN THE BLOOD OF WOMEN

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A SIMPLE procedure for the demonstration of estrogenic substances* in blood was described in two previous communications (Fluhmann[1, 2]). This test depends on the induction of "mucification" of the vaginal epithelium of adult spayed mice by the injection of untreated blood serum, and has now been employed in more than 1,000 instances in the Stanford Gynecological Laboratory. The present report is a further analysis of our experiences with this method and its application to the study of various menstrual disorders.

TECHNIC

A few changes have been made in the technic of the test since it was first employed, the most important of which is a shortening of the period of injection from seventy-two to forty-eight hours.

The blood is obtained by venipuncture and immediately placed in a test tube for transmission to the laboratory. From 25 to 40 c.c. are taken each time. The clear serum is secured by centrifugalization, and the cells are discarded. If it is kept sterile, the serum may be left in the ice box for days and even weeks without losing its potency.

The animals used are adult female mice† which have been spayed six to seven days prior to the day the test is begun. This is important, for if the period of castration is shorter the vaginal mucosa may show unusual changes difficult of interpretation at the end of the test, while if it is longer the mice are not as sensitive to the action of estrin. The usual procedure has been to do a bilateral oophorectomy on the mice on a Tuesday and to begin all tests on the same day of the following week.

A total of 4.5 c.c. of blood serum is given to each mouse, and the test is completed in forty-eight hours. The serum is administered subcutaneously in the back, and the site of each injection is varied as much as possible to facilitate absorption. Three injections of 0.75 c.c. are given daily, at 8:00 A.M., noon, and 5:00 P.M., for two consecutive days. On the third morning the animal is sacrificed and the vagina is carefully dissected free. This is a simple procedure and is accomplished by first making a long incision in the abdominal wall and separating the symphysis pubis. The vagina is fixed in formalin, mounted in paraffin, and transverse sections are made at different levels and stained with hematoxylin-eosin.

The changes elicited in the mouse vagina were previously described with complete photomicrographs (Fluhmann[2]). According to the amount of estrin present, six reactions are recognized:

Reaction 0: Atrophy of the vagina. Mucosa shows two layers of low cuboidal epithelium. Occasional leucocyte.

*The terms "estrin," "estrogenic hormone," and "estrogenic substances" are used synonymously in this report as generic names for the hormone or hormones in the blood of women which induce estrous changes in the vagina of the spayed rodent. The exact chemical nature of these factors has not as yet been determined.

†Since mucification in rats does not develop as readily as in the mouse, they are not suitable animals for this test.

Reaction 1: Vaginal mucosa shows two layers, a basal of low cuboidal epithelium and a superficial of tall columnar cells. A few leucocytes.

Reaction 2: The superficial cells are high, begin to show stratification, and secrete mucus. There is a well-marked increase in leucocytes which may also be found in the lumen of the vagina.

Reaction 3: The epithelium of the vaginal mucosa is composed of several layers, and the cells at the surface are of the mucified variety. A characteristic feature often observed is a folding-in of the mucosa, a type of festooning, which is evidence of rapid growth. The mucosa is invaded by large numbers of leucocytes which also occur in the lumen along with epithelial débris.

Reaction 4: The mucosa is made up of from 6 to 8 or 10 rows of cells, the lower resembling the basal cells of squamous epithelium while those at the surface are still of the tall mucified variety. Leucocytes have disappeared, or are present in small numbers.

Reaction 5: The vagina is now lined by fully developed squamous epithelium with cornified cells at the surface. There are no leucocytes. Since the test is completed in forty-eight hours, a reaction given as 5 may consist of mucified cells at the surface, with cornification just appearing between the surface and the lower stratified layers.

As in all biologic procedures, individual mice vary greatly in their responses to the same dosage, and in this work two or three mice were the minimum employed for each test. After the response for each mouse has been estimated, the numbers are added and then divided by the number of mice used in order to give the reaction. For instance, if three mice are used for a test and reactions 3, 3, and 2 are observed, the reaction elicited by that specimen would be given as 2.7, or three-plus.

On the basis of tests performed with known amounts of estrogenic substance (theelin—Parke, Davis & Co.), and since Kemp and Bjergaard[3] showed that estrin is equally distributed between the red blood cells and the plasma, the average reactions in terms of mouse units per 100 c.c. of whole blood are roughly interpreted as follows:

Average reaction 0 to 1.0 = negative
Average reaction 1.1 to 1.5 = one-plus = traces of estrin
Average reaction 1.6 to 2.4 = two-plus = ±3 M.U. per 100 c.c.
Average reaction 2.5 to 3.4 = three-plus = ±6 M.U. per 100 c.c.
Average reaction 3.5 to 4.4 = four-plus = ±12 M.U. per 100 c.c.
Average reaction 4.5 to 5.0 = five-plus = ±24 M.U. per 100 c.c.

ACCURACY OF TEST

The chief sources of error in the use of the test arise from the variations that occur in the responses of individual mice, and the problem of correctly interpreting the degree of change induced in the vaginal epithelium. The first difficulty is offset by employing as many animals as the amount of blood serum will allow, and the second by having all the tests judged by a single observer. It is desirable that a proper standard be established, and anyone desiring to conduct this test should first study a large series of mice injected with known amounts of estrin at various dose levels.

In order to determine the sensitivity of the test, a series of 94 mice was injected with known amounts of theelin (Fluhmann[2]). The result proved very satisfactory, and as a further check, a second series of 63 animals was recently similarly treated. The theelin was given in aqueous solution at different dose levels, and the injections were conducted in the same manner as in the tests with human blood. The results are given in Table I. It is seen that a dosage of one or two mouse units uniformly

TABLE I

DILUTION	MOUSE UNITS	REACTIONS										AV. REACT.	
C	2	5	5	5	5	5	5	5	5	5	5	5.0	
D	1	5	5	5	5	5	5	5	5	5	5	5.0	+ + + + +
E	½	4	4	4	4	3	4	3	4	2		3.6	+ + + +
F	¼	2	4	3	3	4	3	4	2	3	2	3.0	+ + +
G	⅛	2	3	2	2	3	2	1	2	1	1	1.9	+ +
H	1/16	2	0	1	1	1	1	1	2	2		1.2	+
	0	1	1	1	0	0						0.6	0

gave reaction 5; one-half mouse unit gave an average reaction of 3.6 (four-plus); one-fourth unit elicited an average reaction of 3.0 (three-plus); one-eighth unit, average reaction of 1.9 (two-plus); one-sixteenth unit, average reaction of 1.2 (one-plus); and five uninjected controls gave 0.6 (negative). A study of the responses in individual mice shows that a high degree of accuracy may be obtained even when only two or three animals are employed, and also that the number of errors increases as the dosage of estrin diminishes.

RESULTS

The present study is based on 401 determinations which have been conducted in 84 women and 15 prepubertal girls, and does not include cases previously reported. The patients, unless otherwise stated, had no organic pelvic disease but were under the care of the Endocrine Division of the Women's Clinic for various "functional disorders." With the exception of the group of preadolescent children, a series of examinations was made in each case at intervals of from three to ten days in order to establish a "blood-estrin curve." The arrangement of the cases in this report was made according to the menstrual history rather than the clinical diagnosis, since this gave a greater uniformity in the results.

PREPUBERTAL GIRLS

The blood of 15 normal girls varying from four to ten years of age was examined for the presence of estrin by the mucification test. The results are given in Fig. 1, and it is seen that they are very consistent. Of 8 children seven years of age or younger, only one, a girl of seven, gave a positive reaction. On the other hand, 7 blood tests in girls eight to ten years of age gave a two-plus reaction in 5 instances, a one-plus once, and a negative once. These findings are significant because secondary sexual characteristics appear between the ages of eight and ten years. At this time the differentiation of the female pelvis begins and there is also the growth activity of the mammary tree, which precedes the gross development of the breasts (Howard[4]).

MENSTRUAL CYCLES OF TWENTY-FIVE TO THIRTY DAYS IN LENGTH

This group is composed of a series of 12 women whose menstrual cycles, at the time of examination, were twenty-five to thirty days in length. A total of 14 blood estrin curves based on 62 tests are available for study. Seven of the patients complained of dysmenorrhea, one of dysmenorrhea and sterility, one of irregular delayed menses, one of polymenorrhea, one of underdevelopment of the breasts, and one was a normal control.

In a previous report (Fluhmann[2]) a composite curve, based on the examination of 80 specimens obtained from 46 patients at various stages of the cycle, showed an increase in the amount of estrin in the blood during the midinterval, with a secondary rise at the time of menstruation. This result has been accepted as the normal, and a study of the individual blood estrin curves in this group shows a close agreement with this standard. In spite of wide variations, the most constant finding was that of a rise in the concentration of estrin in the blood occurring from

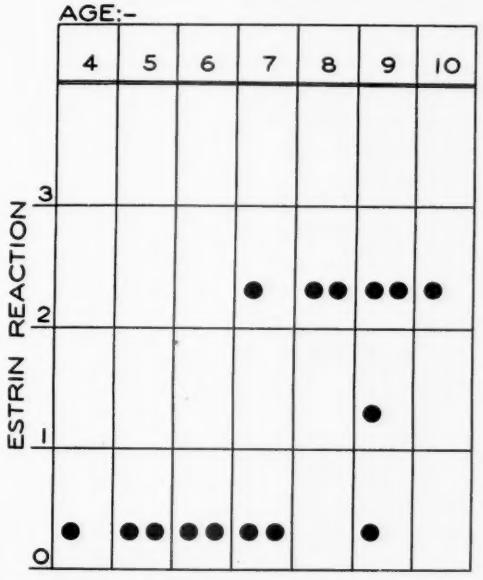


Fig. 1.—Estrogenic substances in the blood of 15 prepubertal girls.

eight to eighteen days before the onset of menstruation (Figs. 2 and 3). This peak was noted in 11 out of 14 curves, and in addition a secondary increase within four days or actually at the time of menstruation was observed in 5 of these cases (Fig. 3). In 2 instances, the only rise was found during the three days preceding menstruation, and in one traces of estrin or negative tests were obtained throughout the whole cycle.

One patient became pregnant while a series of tests was being conducted. A negative result was obtained on the sixth day, a two-plus on the twelfth and eighteenth days, negative on the twenty-sixth day, and finally a four-plus on the sixty-fifth day following the first day of the previous menses.

It would seem that these results are not in keeping with the blood estrin studies of Frank and Goldberger,[5] Mazer and Goldstein,[6] Siebke,[7] and others. These authors, who employ a method based on the chemical extraction of estrin from the blood, find a consistent positive test only during the seven days preceding the menses, while it is not demonstrable at other times. The rise in the midinterval

and the secondary increase just before or at menstruation, which have been observed with the mucification test, however, show much similarity with the total daily urinary excretion of estrin at various stages of the cycle. For instance, Loewe and Langes noted an increase in the urinary excretion ten to twelve days after menstruation. Frank[9] states, "considerable variations are encountered, but two periods of maximum excretion, the first corresponding to the theoretical time of full follicle ripening

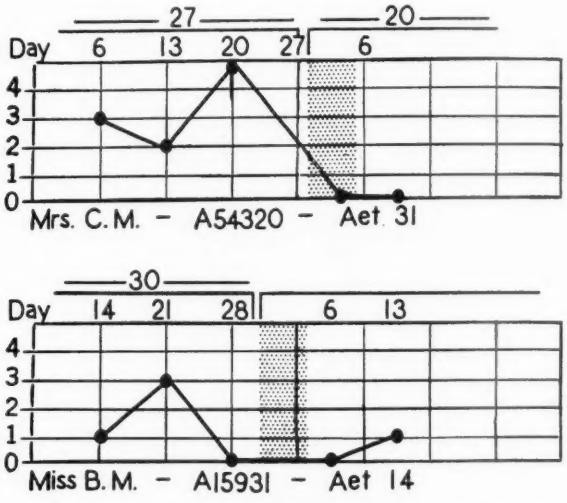


Fig. 2.—Blood estrin curves of patients with menstrual cycles twenty-five to thirty days in length.

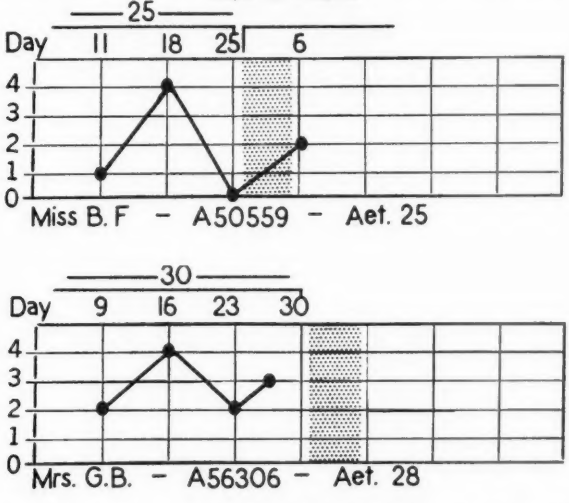


Fig. 3.—Blood estrin curves of patients with menstrual cycles twenty-five to thirty days in length.

or ovulation (fourteenth day), and the second in the last week preceding the menses, are characteristic." Siebke[7] found the highest excretion ten and eleven days before menstruation. The figures given by Zondek[10] for the various stages of the cycle show the highest amounts (300 mouse units per liter) from the nineteenth to the twenty-first days as compared with 50 to 70 units at other times. In a recent study, conducted with one subject over a period of some months, Gustavson and

Green[11] found an increased estrin content in the urine from the ninth to the twelfth days following menstruation, and a secondary rise from the fourteenth to the twenty-first days.

MENSTRUAL CYCLES OF THIRTY-ONE TO FORTY DAYS IN LENGTH

Thirty-eight tests were performed on 8 patients with menstrual cycles ranging from thirty-one to forty days in length. Three of these patients reported for investigation with the complaint of "irregular delayed menses," three complained of sterility, and two of dysmenorrhea.

A midinterval increase in estrin concentration was observed in every case (Fig. 4). In 2 instances it was found on the seventh and eleventh days, respectively, before menstruation, while in 6 it varied from fourteen to twenty-one days before the succeeding period. A secondary rise occurred on the first day of the menses in one case. The curves in this group thus conform to those of women with cycles of twenty-five to thirty days in length, but the greatest concentration was found somewhat earlier in the interval.

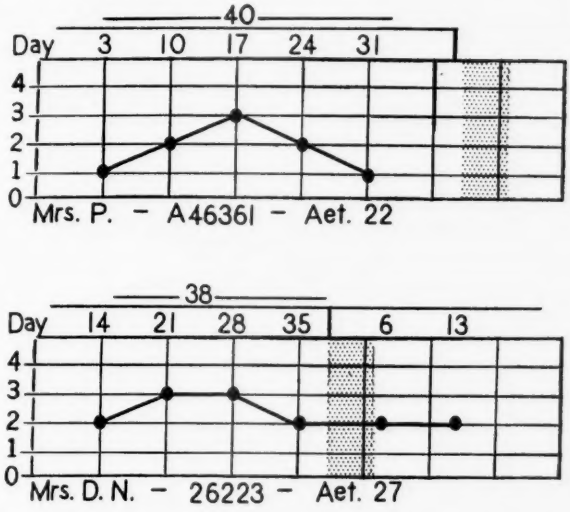


Fig. 4.—Blood estrin curves of patients with menstrual cycles thirty-one to forty days in length.

SCANTY MENSTRUATION

Four patients with cycles varying from twenty to thirty-six days in length complained of "scanty menses." Fifteen tests were performed and again a constant midinterval rise in estrin concentration was observed, while one patient showed a premenstrual rise which occurred on the last day of a twenty-two-day cycle. No indication was found that such cases should be considered as "hypoovarian" in the sense that smaller quantities of estrogenic substances are found in the blood.

ANOVULATORY CYCLES

It was hoped that a large series of patients with "anovulatory cycles" could be studied from the standpoint of estrin content of the blood, but technical difficulties made it a very elusive task. The diagnosis is dependent on demonstrating an "estrin phase" in the endometrium just before or during an apparently normal menstrual period, and since the tests must be performed in the weeks preceding the

actual flow, the choice of patients became a question of guesswork or chance. It also seemed correct to eliminate from this group individuals with profuse bleeding who showed a characteristic hyperplasia endometrii. For these reasons, only four patients were available, and in each case the diagnosis of "anovulatory cycle" was made from the examination of biopsy specimens of the endometrium obtained just before or at the onset of a period of bleeding which to patient and doctor seemed to be a "normal menstruation" at the expected time. The specimens of endometrium were obtained with a Hoffmann curette[12] and we believe that the bleeding was not an unusual event precipitated by this minor operative procedure.

Fourteen tests were done on the four patients, but the curves do not show any consistent pattern which can be considered characteristic for this type of cycle. In

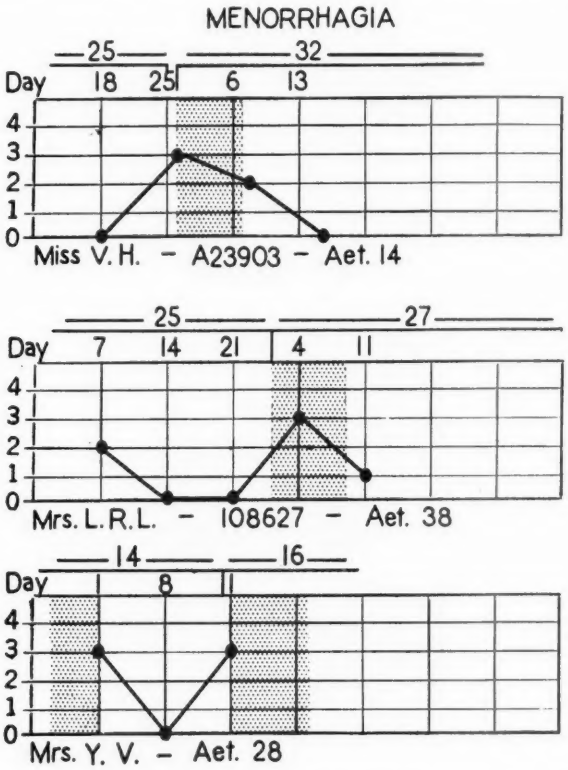


Fig. 5.—A characteristic of the blood estrin curves of some patients with menorrhagia or polymenorrhea is an increase in the concentration of the hormone at the time of onset of the bleeding.

one case three tests were negative or showed merely traces of estrin. A second gave two-plus and three-plus reactions on the fourth, thirteenth, and twenty-fifth days of a twenty-seven-day cycle. The third gave a rise in estrin concentration three days, and the fourth fourteen days, before the onset of menstruation. The findings must therefore be considered as inconclusive.

MENORRHAGIA AND POLYMENORRHEA

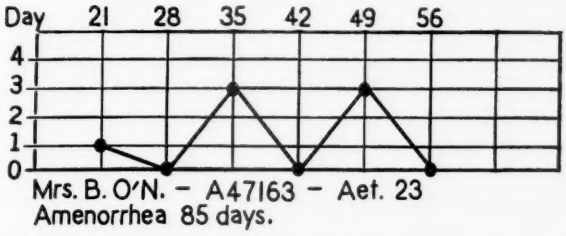
Seven patients complaining of profuse menstrual periods were examined, and of these, 3 were young girls of thirteen to seventeen years of age. Thirty tests were performed, and of the 7 blood estrin curves, 5 showed a striking picture which

differed from the normal standard. The peak of estrin concentration was found associated with the onset of the bleeding and then gradually decreased as the flow diminished (Fig. 5). Of the two exceptions presenting the normal midinterval rise in estrin concentration, one was a patient in whom the bleeding was attributed to an old pelvic inflammatory disease and not to a "functional disorder."

Four patients complained of polymenorrhea, cycles shorter than twenty-five days, in addition to profuse flow, and 15 tests were conducted in this group. Two of these again showed a marked increase in the amount of estrin in the blood at the time of the onset of the bleeding (Fig. 5).

HYPERPLASIA ENDOMETRII

Twenty tests were conducted in 5 patients with irregular or profuse uterine hemorrhage associated with the histologic picture of hyperplasia endometrii. In 3 cases the blood estrin curves showed a sharp rise in concentration at the time of onset of the bleeding and a decrease with the cessation of the flow. One patient was examined



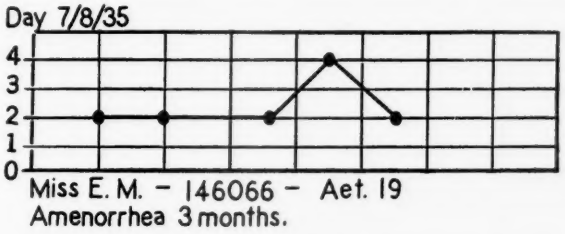


Fig. 6.—Type I curves of patients with amenorrhea.

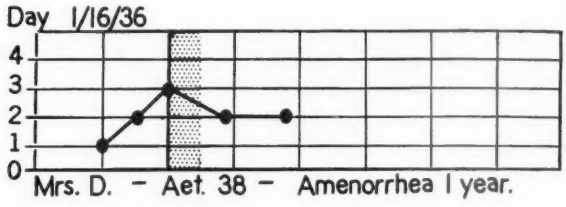
sixteen days and eight days before the onset of a profuse period and showed a one-plus and a negative reaction. In another case, 3 tests demonstrated a sharp increase in the estrin content over a period of five days following a curettage, but no subsequent history is available.

The results of the blood examinations in this group and in the patients with menorrhagia suggest that certain cases of "functional" uterine hemorrhage are associated with an increase in the concentration of estrogenic hormone in the blood at the time of the onset of the bleeding. These findings are confirmatory of the blood studies of Siebke[7] and the urine determinations of Frank and others.[13]

AMENORRHEA

This group represents the largest of this series and consists of 119 tests, 26 blood estrin curves from 22 patients. The association of other hormonal tests and clinical findings with the estrin studies is reserved for a future publication, but the results fall into three distinct groups:

1. *Type I Curves (Cyclic).*—In this category are 16 curves from 13 patients in whom there was a recurrent increase and decrease in the amount of estrogenic substances in the blood (Fig. 6). The rise generally occurred every two to three weeks and was as great as that observed during the midinterval in normal individuals. In 8 cases a period of uterine bleeding set in either during the period of observation or



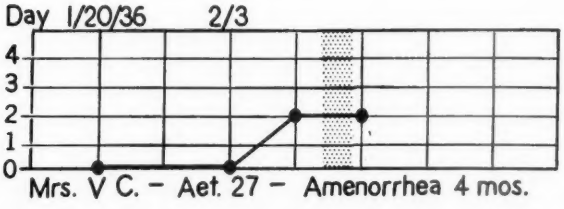


Fig. 7.—Curves illustrating increase in the concentration of estrin in the blood at the onset of uterine bleeding following a period of amenorrhea.

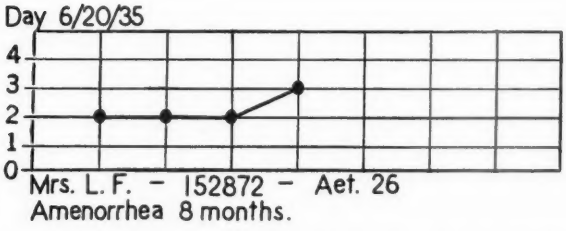


Fig. 8.—Type II and Type III curves in amenorrheic patients.

shortly afterward, and in 4 patients there was a rise in estrin concentration associated with the onset of the flow (Fig. 7). This observation may mean that such bleeding following amenorrhea does not necessarily represent a normal menstrual period, but an abnormal uterine hemorrhage.

2. *Type II Curve.*—In 4 instances no clear cycle could be demonstrated, but all tests gave a two-plus reaction with an occasional increase to three-plus or a decrease to one-plus or negative (Fig. 8). These patients therefore must be considered

as having a small but appreciable amount of estrogenic hormone constantly present in the blood. Of special interest in this group was a patient with an amenorrhea of seven and one-half years' duration, attributable to a hypophysial tumor associated with acromegalic changes.

3. *Type III Curve.*—This group is illustrated by 6 blood estrin curves (5 patients) in which reactions 0 and one-plus were found in all tests, with only an occasional exception (Fig. 8). The amenorrhea is thus associated with a persistent absence of estrin from the circulating blood. The only case of primary amenorrhea in this series, a patient of Dr. R. Glenn Craig, belongs to this category, and is illustrated in Fig. 9. It is interesting that the administration of a pituitary gonadotropic hormone (Prephysin-Chappel) resulted in a sharp rise in the blood concentration which persisted for two weeks. However, menstruation did not ensue and 3 successive tests gave negative findings.

The patients with amenorrhea of longer and shorter duration may thus be divided into 3 groups according to the blood estrin determinations. In the majority

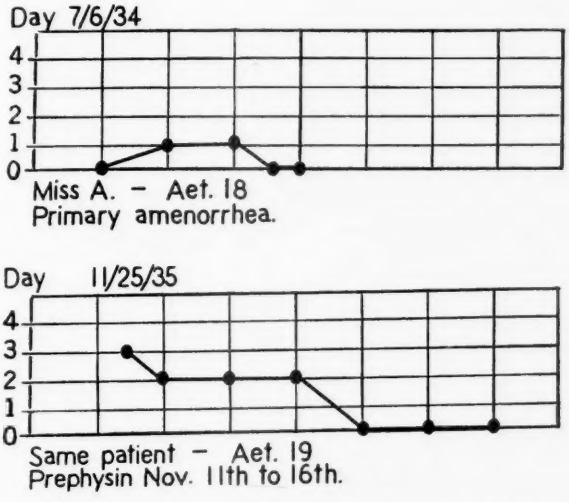


Fig. 9.—Patient with primary amenorrhea. Type III curve with increase in blood estrin following administration of a pituitary gonadotropic preparation.

there is a cyclic rise and fall in the amount of estrin present; in a smaller group there is a constant moderate amount of estrin in the blood; and in a third category are women with a total absence of demonstrable estrogenic hormone.

POSTCASTRATION

Since it has been assumed that estrogenic substances are primarily "ovarian hormones," it was of special interest to study the blood of women in whom bilateral oophorectomy had been performed. Twenty-eight tests were conducted on 8 patients, 5 of whom were under the age of forty and 3 from fifty to fifty-two years old. The time from the operation to the period of observation varied from five weeks to ten years. In all cases it was possible to demonstrate the presence of estrin in the blood in amounts comparable with those seen in normal individuals (Fig. 10). A cyclic increase and decrease of the hormone was noted in 4 cases, while in 4 the blood showed two-plus and three-plus readings, such as noted in the Type II curves of the amenorrheic patients. Although these results may seem startling, they are again in conformity with reports on the presence of estrin in the urine of castrates (Loewe and others,[14] Laroche and others,[15] Frank and others.[16]).

MENOPAUSE AND POSTMENOPAUSE

Sixteen observations were made on 3 patients complaining of menopausal vasomotor symptoms, in whom the menstrual periods were scanty or occurred at delayed intervals. In all instances a cyclic rise and fall of estrin was demonstrable, and

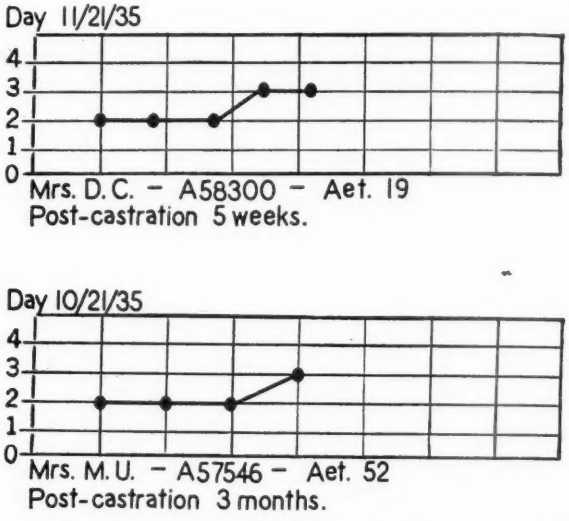


Fig. 10.—Estrogenic hormone in the blood of women following bilateral oophorectomy.

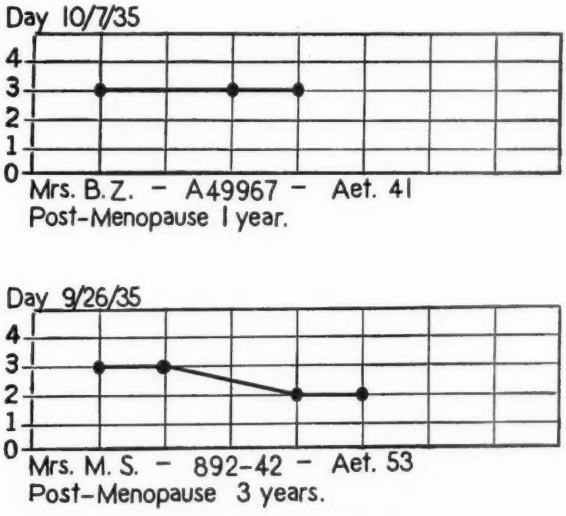


Fig. 11.—Estrin in the blood of women in the postclimacteric period.

although some irregularities were noted in the curves the observations are too few to determine any definite abnormality. It is interesting that 2 out of the 3 patients showed an increase in the amount of anterior pituitary hormone in the blood when tested with immature mice by the method previously described (Fluhmann[17]).

Nine tests were done on 2 patients with menopausal symptoms in whom a unilateral oophorectomy had been previously performed. In both instances a cyclic

occurrence of estrin, with peaks of three-plus, was demonstrated and in one there was also an increase of anterior pituitary hormone.

Fifteen tests were conducted on 4 patients who had passed the menopause from one to three years. In corroboration of the studies made with urine by Zondek,[10] Kurzrok and Ratner,[18] and Frank and others,[16] it was possible to demonstrate appreciable amounts of estrin in the blood. In two cases the curves showed the presence of a cycle, while in two the results gave two-plus and three-plus reactions as in the Type II curve of the amenorrheic patients (Fig. 11). A positive test for the anterior pituitary gonadotropic factor was obtained in two patients whose blood was examined for this hormone.

DISCUSSION

One of the important developments of modern endocrinological investigation has been the use of various tests for the presence or absence, increase or decrease, of hormones in the blood, urine, or tissues. In the case of the Aschheim-Zondek test for the chorionic gonadotropic hormone, the results have been of invaluable assistance in the management of certain clinical problems. The methods which have been described for determining the presence of anterior pituitary sex factors and estrogenic substances have not proved of such practical value, but they have furnished new ways of studying the physiology and pathology of the reproductive cycle.

The Allen-Doisy test for estrin is a well-established laboratory procedure, but the relatively small amounts of hormone in blood or urine require chemical extraction before the biological examination can be conducted. In the case of blood, this means a laborious preparation which yields sufficient material to inject only one or two test animals. These difficulties call for a more efficient and less complicated procedure, and although the "mucification test" also presents disadvantages it may be considered as an alternative method.

It is difficult at present to reconcile the differences which this test has given when compared with the results obtained with the Frank-Goldberger method. It is possible that some explanation will be found when further chemical analyses are available, but, as pointed out previously, there are a number of important observations which suggest that the blood estrin curves obtained with the mucification test compare more favorably with our knowledge of the activity of estrogenic hormones in physiologic conditions. (1) The occurrence of the peak of estrin concentration in the blood during the early part of the second half of the normal menstrual cycle would seem to be associated with ovulation. This observation is in keeping with the incidence of ovulation at the time of estrus, which in the lower animals is the climax of estrin effects. (2) The intensity of spontaneous rhythmic contractions of excised human fallopian tubes apparently follows that of this estrin curve, since Snyder and Seckinger[19] found the greatest activity in the middle of the interval. (3) The studies of Allen and others[20] on the estrin

content of human ovarian tissues gave results definitely related to the blood estrin curves, and although the amount of hormone present in the ovary is not necessarily a true index of the total produced by that organ, the concomitant findings are at least very suggestive. They obtained high yields of the hormone from recent corpora lutea removed on the thirteenth to the seventeenth day of the menstrual cycle, and there was a considerable decrease by the twentieth to the twenty-second day. (4) A characteristic of the menstrual cycle of monkeys, which is pronounced in baboons and chimpanzees (Zuckerman[21]), is a swelling and deep reddish discoloration of the skin of the external genitalia. This is an estrin effect, and it reaches its maximum intensity at about the middle of the cycle or near the time of ovulation. (5) And finally, it has been shown throughout this report that the blood findings are definitely comparable with the results obtained from the study of the daily estrin concentration in the urine.

It is impossible at the present time to properly interpret the significance of the presence of estrogenic substances in the blood of women. These hormones have been considered as ovarian in origin, and the cyclic increase and decrease which occurs during the course of the menstrual cycle points to a close association with follicular activity. Their appearance in the blood of preadolescents at the time that the secondary sexual characteristics begin to develop is also in favor of a gonadal source. On the other hand, the occurrence of estrin in the blood and urine of castrates and of women in the postclimacteric is a conclusive demonstration that it must have an extraovarian origin. As Zondek[10] has shown, it does not seem likely that an amount of the hormone sufficient to give the blood and urinary findings which have been reported comes from the ingestion of food containing estrin. In any case, the incidence of estrin in the blood in association with involutional changes in the uterus and vagina shows that in these individuals it does not exert the same hormonal activity which is manifested in the presence of functioning ovarian tissue. The question must remain *sub judice* for the present, but the solution may come from further chemical studies on the nature of the estrogenic substances present in the blood and urine.

SUMMARY

1. The technic of the mucification test for the demonstration of estrogenic substances in blood is described, with a few modifications.

2. The examination by this method of solutions containing known amounts of theelin at various dose levels showed a high degree of accuracy.

3. The present report is based on the examination of 401 specimens of blood from 84 women and 15 prepubertal girls.

4. The blood of 5 out of 7 normal girls between the ages of eight and ten years gave positive reactions for estrin, whereas the tests were negative in 7 out of 8 girls from four to seven years of age.

5. In 22 out of 25 patients it was found that during the course of the menstrual cycle there was an increase in the concentration of estrin in the blood, which occurred during the midinterval and seemed to be associated with ovulation. A secondary rise just before or at the onset of menstruation was noted in seven instances.

6. No characteristic variations were observed in 4 patients with anovulatory cycles.

7. In 10 out of 16 cases of menorrhagia, polymenorrhea, or uterine hemorrhage due to hyperplasia endometrii, a rise in the concentration of the blood estrin was observed at the onset of the bleeding.

8. Three types of blood estrin curves were found in patients with amenorrhea. (1) There was a cyclic rise and fall in the amount of estrin. (2) A constant moderate amount of estrin was present. (3) There was a persistent absence of demonstrable estrogenic hormone.

9. Estrogenic substances were found in the blood of women following castration and in the postclimacteric period.

10. The presence of estrin in the blood was demonstrated in association with increased amounts of anterior pituitary sex hormone.

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My thanks are due the members of the Pediatrics Department for obtaining specimens of blood from the prepubertal girls; to Dr. G. F. Jones, Dr. K. M. Murphy, and Dr. L. M. Bayer for their cooperation in the study of the patients; and to Mr. John J. Kan and Mr. Pierre Lassegues for their technical assistance in conducting the tests.

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Stanford University Hospital

DISCUSSION

DR. OTTO H. SCHWARZ, St. Louis, Mo.—My associate, Dr. Soule, has been very much interested in the separation of the hormones in the blood of the human being. I shall read from his notes.

"We have utilized Dr. Fluhmann's method for studying the presence of estrogenic hormones since the spring of 1935. At this time we should like to discuss the problem of the passage of hormones across physiologic barriers.

"The question of the presence of hormones in the fetal circulation has been a problem of extensive study. Various investigators have demonstrated that adrenalin, insulin, posterior-lobe pituitary, and parathyroid hormones are *not* transmitted through the placenta. Schlossman (1932) discussed the entire problem of interchange of substances between mother and fetus through the placenta.

"With regard to the sex hormones, we have demonstrated that the anterior-pituitary or anterior-pituitary-like hormone which is responsible for the "positive" Aschheim-Zondek or Friedman test is *not* present in the human cerebrospinal fluid. More recently, by utilizing this same "rabbit" test, we demonstrated that this pituitary or pituitary-like factor is not transported through the human placenta. This was shown by performing rabbit tests on maternal blood serum and fetal cord blood serum. These specimens were taken simultaneously at the time of delivery and the tests carried out in the routine manner. In *no* case were we able to demonstrate "blutpunkte" with cord blood serum even though we used two or three times as much cord blood serum as maternal serum. The obvious conclusion is that this anterior-pituitary or pituitary-like hormone does *not* pass the placental barrier.

"Various methods for the demonstration of estrogenic hormones have been tried by many observers. In most instances these technics have either proved wanting in accuracy, too complex, or not sufficiently consistent.

"So far as the demonstration of estrogenic hormones in the maternal and fetal circulations is concerned, the literature is rather sparse. Schlossman quotes several authors and concluded that folliculin is present in the fetal as well as in the maternal circulations. He does not attempt to answer the question as to whether it is present as a substance transported through the placenta or whether it is a product of the placenta itself. Skowron and Skarzyuski concluded that in rabbits the follicular hormone passes through the placenta.

"By using Fluhmann's method for the study of estrogenic hormones as originally described in 1934, we continued our study of the interchange of hormones through the placenta. Fetal cord blood and maternal blood taken simultaneously were tested by this method. Various dilutions of these serums from full strength to 1:20 were tested and in all tests it was found that these hormones gave the *same* degree of reaction in both maternal and fetal samples. This is a most interesting observation in view of the knowledge that other hormones are not transported across the physiologic barrier.

"We have also used Dr. Fluhmann's method for the study of various endocrine problems, particularly the menopause state and various amenorrheas. Our present approach is to make a blood study by this technic and a parallel study of an endometrial specimen *and* the vaginal mucous membrane. The data concerning this work is as yet not ready to be reported."

DR. EMIL NOVAK, BALTIMORE, MD.—In Dr. Fluhmann's interesting study, some of the results he reports clarify our clinical and histologic impressions, while others are rather confusing. The finding of estrin in prepubertal phases is in line with the results of others, and also with the fact that follicle development occurs long before the age of puberty. In amenorrhea one may find a very trophic endometrium, or one may find, as we have done in a few cases, an endometrium which apparently passes through a cycle identical with that of the normally menstruating woman except for the bleeding phase. Just what replaces the latter is an interesting problem which remains to be worked out, although it should not be a difficult one in view of the present-day use of the endometrial biopsy.

I was much interested, too, in Dr. Fluhmann's frequent finding of estrin in women after the menopause or after castration, an observation which likewise conforms to the findings of others. It also fits in with the fact that proliferative endometria, and even hyperplasia, may be found in elderly women long after the menopause, an observation upon which I hope to elaborate in my own paper tomorrow. I have been more and more impressed with the fact that the term "senile endometrium" is only a chronologic one, for it may include not only the atrophic type, but also pictures indicating all degrees of proliferative activity, presumably as the result of an estrogenic stimulation of some sort, though we do not know its source.

DR. SAMUEL H. GEIST, NEW YORK, N. Y.—In order to correct an impression that one may possibly have received from what Fluhmann said, I wish to point out that Frank's results do not differ so very much from those of Fluhmann as determined by his new method. The mucification of the vagina was first regarded as a specific effect of the corpus luteum. Later it was ascribed to injection of estrogenic substances. As we now know, there are probably a number of estrogenic factors in the organism, either in free or combined form. It is quite possible that the mucification reaction is influenced by one or the other of these factors to a greater degree than the vaginal smear reaction. This may account for some discrepancies between the results obtained by the Frank and the Fluhmann reaction.

In a series of amenorrhea cases, some primary and some secondary, the same picture was obtained as Fluhmann showed in his slides. There were certain individuals who showed a very low level of hormone, whereas others showed a definite cycle. In those cases that were associated with bleeding and shortened intervals, the same picture was obtained in many of Frank's cases where just before the onset of the bleeding, or while the bleeding was in progress, a greatly increased amount was present in the urine but none or only small amounts in the blood. In the menopause cases, in spite of very active menopause symptoms, some women show a considerable amount of estrogenic hormone in the blood and urine. In addition the biopsy investigation of the vaginal mucosa was more or less in conformity with the hormone excretion. Some of the cases that had symptoms and excreted hormone still showed perfectly normal vaginal mucosa. There is therefore not so great a difference or contradiction between Frank's work and that just reported, as one might have gathered from Dr. Fluhmann's remarks.

DR. FLUHMANN (closing).—I did not wish to give the impression that all of my results were contradictory to those reported by Frank. What I had chiefly in mind was Frank's finding that estrin rises in the blood from three to seven days before normal menstruation, whereas in my studies this rise seems related to ovulation rather than menstruation. It should also be said that it is not right to speak of a "contradiction," because the estrin determinations in the two investigations were made by widely different methods.

It is a temptation to speak in more detail of the clinical aspects of this work, but at this time it would be hazardous to do so. However, I should like to refer to its application to our present concept of the cause of menstruation. As you know, Allen's "estrin-deprivation" theory seeks to explain the occurrence of uterine hemorrhage as due, not to a direct action on the uterine mucosa, but to the removal of ovarian influence following its stimulation of endometrial growth. From my studies with blood-estrin determinations it appears that uterine bleeding may take place at a time when there is a high amount of estrogenic substances in the blood and conversely a rise and fall of the hormone content may be associated with amenorrhea. These results may be open to several interpretations, but it at any rate seems probable that estrin-deprivation *alone* is not sufficient to account for the occurrence of menstruation, and other factors must also play a part in the normal menstrual cycle.

TOTAL VERSUS SUBTOTAL HYSTERECTOMY

A Clinical and Technical Study

J. R. Goodall, M.D., Montreal, Que.

THIS is merely an expression of opinion based upon personal experience arising out of 550 consecutive cases of hysterectomy, about equally divided into the two categories. The two series are as alike as possible in every circumstance and antecedent. In the first half of the series, the subtotals markedly preponderate. As my experience and finesse improved, the totals greatly outnumbered the subtotals, so that for the past year, the total hysterectomies constitute about 90 per cent of all my hysterectomies. The uterine pathology included all the common diseases. Many were complicated by appendage troubles of almost every variety. The uterine preponderant diseases were fibroids, fibrosis, corporeal malignancy, advanced cervical disease, chiefly in the third and fourth decades, and states of pelvic allergy associated with uncontrollable uterine hemorrhage. There were only five cases of cervical cancer, after treatment by radium, in which hysterectomy was deemed advisable.

I wish to state most emphatically that it is fartherest from my intention to force the unskilled gynecologic surgeon into an operation, graver than that for which he is fitted by experience. But to the skillful surgeon, to whom a slightly longer operation presents no greater deterrent than the extra time that is expended, the total hysterectomy, *caeteris paribus,* will present great advantages to the patient, as well as great surgical satisfaction.

There are advantages and disadvantages to each of the two types of hysterectomy.

The disadvantages of total hysterectomy are:

1. Greater time expended at operation.
2. Greater skill required.
3. Greater blood loss.
4. Greater danger to vital organs.
5. Greater difficulty if the pelvic organs are fixed deeply in the pelvic cavity, or if patients are obese.

The advantages of total hysterectomy are:

1. Fewer immediate postoperative complications.
2. Fewer remote sequelae.
3. Smoother recoveries.

The disadvantages require no further elucidation. I believe they will receive general acceptance. On the other hand, the advantages may require considerable discussion.

The average difference between a subtotal and total hysterectomy is between five and fifteen minutes, a negligible factor in the average case. The skill required is merely that derived from experience, preferably primarily derived from one who has perfected the technic, with an accurate knowledge of the relative and absolute propinquity of the vital pelvic structures, and care in avoiding undue tension upon tissues. Tension is one of the greatest deterrents to forming union, and one of the most frequent causes of postoperative pain. The great onus of care in these cases surrounds the invisible ureters. To some they become a mental bogey. A ureteral complex, you will excuse the term, is one of the worst of emotional acquisitions in the surgeon. Some men seem to be unable to avoid them, and their mental stress to go wide of them seems to act like a lodestone.

To the best of my knowledge, I have never injured a ureter or bladder in hysterectomy. That does not mean that it has not happened, but merely, if it did, it was not only unobtrusive, but not even recognizable when sought. Operative bladder injuries are rarer than ureteral complications, in the experience of the general run of gynecologic surgeons. It is my experience that it is extremely difficult to injure the bladder when it is empty and contracted. It is one of the most elusive organs.

The difference in the blood loss in the two types of operation may be negligible. In the ordinary run of cases it is so. But it can be considerable, especially in hemorrhagic cases, or when a clamp or suture fails in its requirements. A word of caution here may not be amiss. A careful preoperative inquiry into the patient's history, as to untimely or copious uterine hemorrhages, nosebleeds, migraine, and familial history of vascular instabilities, may make one cautious in carefully suturing raw surfaces completely, and insisting upon a most thorough hemostasis. Where the history is at all suggestive of a hemorrhagic state, the usefulness of a preoperative blood transfusion and a repetition of the same on the seventh day after surgical intervention will obviate the serious oozing at operation, and prevent late postoperative bleeding. It is a singular fact that vascular unstables are prone to develop an advanced state of hemorrhagic tendency about the eighth day. This, though frequently occurring as an expression of a low state of sepsis, is also a sequel of low platelet count at that period, and, in most cases, can be forestalled by a carefully matched transfusion. These cases should be matched for three-quarters of an hour, and any abnormality should be guarded against. These nonseptic hemorrhagic cases are prone to develop wheals at the point of any hypodermic injection, and other signs of skin irritability. A special paper is being devoted to this important subject. Should the secondary hemorrhage be due to sepsis, it will occur

usually between the eighth and twelfth day after operation. The sepsis is frequently ignored, because the temperature seldom rises more than a fraction above 99° F. and is usually continued over several days. It is in just these types of septic cases that either blood or vessel, or both, becomes so altered by the bacterial toxin, that diapedesis or rhexis occurs. Hemorrhagic states, as previously stated in my monograph on puerperal infections, rarely occur in acutely septic cases, but are most common in the continued cumulative low-grade infections, which do not rouse the body to the formation of antigens. When vaginal hemorrhage occurs, and it has occurred in my series of total hysterectomies in 2.25 per cent of cases, it has always been in these two types of cases: the vascular unstables, both septic and nonseptic; the vagina should at once be cleared of clots and packed gently with gauze with an uterine packer. To leave the vagina filled with clots is tantamount to inviting further bleeding. In every instance, this procedure, preceded by a transfusion, has promptly arrested the bleeding.

Generally speaking, total hysterectomy is easier in the parous than in the nulliparous, due to the greater mobility of the uterus, owing to the lengthening of its ligaments. Low set, fixed uteri may present unusually difficult surgical circumstances. Particularly is this so in cases of subacute or chronic pelvic inflammatory disease. But the difficulty, when overcome, brings a sense of great satisfaction, for it is in just these types of cases that it pays to remove the cervix with its susceptible mucosa.

About 70 per cent of patients who have total hysterectomies void spontaneously after operation, as against 45 per cent of subtotals. This circumstance, confirmed by all my house surgeons in the four different hospitals, seems contrary to all the laws of probability. An explanation has been sought, but nothing satisfying has been forthcoming. Is it that in the subtotal only, certain branches of the autonomic nervous system are severed, and that others are thereby thrown out of normal function; whereas, in the total hysterectomies, the majority, if not all, of the autonomic nervous system to the bladder is severed, causing the bladder, therefore, to become an automaton without sympathetic nervous control? In our present imperfect knowledge of autonomic vesical control and autonomic vesical distribution, it is quite impossible to vouchsafe anything but theories. Consult any work upon the results of section of the sympathetics upon vesical control, and one is led into a perfect orgy of contradictions and confirmations among the experimenters. The low percentage of spontaneous bladder evacuations in subtotals has been explained, by one of my colleagues, upon the basis of an inflammation spreading from the retained cervical stump to the bladder, an explanation that seems quite inadequate for many valid reasons.

Primary hemorrhage has never occurred in any one of the 550 cases, so that in this respect they are equal. Thrombophlebitis is a much more

common complication in subtotal hysterectomies. The comparison is most striking. The percentage was three to one.

In all clean cases, thrombophlebitis may be taken as an index of a man's technic, both in obstetrics and in gynecology. Let this be most emphatically stated. So many, whether from ignorance or self-deception, assume that thrombophlebitis is an unpreventable misfortune, quite beyond their control. There is a ready explanation for the preponderance of thrombophlebitis in subtotals. It is to be found in the cervical mucosa. Just a few lines about pelvic thrombophlebitis. It is rarely diagnosable, except in its secondary complications. It is rarely acute, and most dangerous when of low-grade infection, or in its defervescence after an acute or subacute attack. The general agent of thrombophlebitis is an infection of low virulence and in the vast majority of cases it emanates from a mucosal disease. In this respect, the mucosa of the cervix fills all the requirements. Hence the relatively higher percentage of thrombophlebitis in subtotals, as against totals. The aseptic technic in both operations in my series was essentially the same, so the higher percentage must have been due to an agent residing in the tissues. And now, when upon the subject, it may be opportune to stress something which has not received sufficient attention: inflammatory diseases run very different courses, depending upon the tissues in which they are placed. Infections in mesoblastic and ectodermal tissues usually run a purely local and rapidly conclusive course, or a virulent and rapidly critical stage with an equally rapid cure. Restoration to normal function is usually complete in proportion to the rapidity of the disease, provided the patient survives the storm. In mucosal diseases, however, the great majority are subacute or chronic from their inception. Those that are not tend to become so eventually, and the tendency for the disease to linger indefinitely is the rule. This tendency leads eventually to two distinct changes, hyperplasia or hyperfunction, or both. The virulence dies down, and the corporeal reaction is then seldom sufficiently active to effect a complete cure. Thrombophlebitides are preponderantly mucosal in origin. In the cervical mucosa we have a classical example of these changes, and the organisms of the cervix are ready, in their attenuated form, to become the active agents of thrombophlebitis. That these organisms are still markedly pathogenetic can be clearly shown by the frequent incidence of secondary septic hemorrhage, when cervical amputations and suchlike operations were the vogue. Many of us in those years saw women, ostensibly in the bloom of health, submit themselves to cervical operations, only to be found on the 8th to the 12th day almost at the point of death, through septic hemorrhage. Why? Because we amputated through diseased mucosa. Why the delay to the twelfth day? Because the organism was semivirulent. Many of these cases developed pelvic thrombophlebitis and succumbed to its accidents. Mucosal disease is one of the greatest

menaces to primary union. Can this mucosal menace be removed by cautery? That depends. In many cases, the disease is limited to the mucosa proper, an endocervitis. In others, the organism is invasive, causing a large, hard, cystic cervix, a cervicitis. In still others, there may be combination of both.

In cases of simple endocervicitis, coning out the cervix and cauterizing the residual portion of the canal may be effective. In the cervicitis types, cauterization, except it be very deep and destructive, is more harmful than no cauterization at all. The ideal remedy is total removal, when the skill and experience overbalance the risk.

Drainage was not used at all in any of the cases, and complete closure is a fixture.

Subtotal hysterectomy is often disappointing in its late sequelae. In a goodly percentage of my cases a leucorrhea developed, which did not exist prior to operation. In many cases, endocervicitis and ectropion developed after operation, necessitating treatment. This invariably leads to disappointment in the efficiency of operation. Both the above changes, I believe, can be attributed to the abnormal status of the cervix. Doubtless, in subtotal operations, the cervix must suffer changes in nutrition and nervous impulses, which eventually lead to a state of pathology.

That these abnormal changes are in part dependent upon the menstrual flux is shown by the infrequence of these abnormal developments when both ovaries are removed with the body of the uterus. In five of my patients, there were very troublesome cervical hemorrhages, that came on some months after subtotal hysterectomy. Four of these were operated upon for continuous metrorrhagia, that resisted every form of treatment; none of them showed any appreciable pelvic pathology, either by bimanual examination, or at the time of operation. Two of them had two sterilizing series of deep x-ray, with recurrence of hemorrhages after a period of amenorrhea. One had radium once, and three series of deep x-ray in doses estimated sufficient to sterilize, at least temporarily, if not permanently. It is my practice to cone out the cervix in all subtotals, and I feel very confident that no endometrium had remained, unless it had invaded the domain of the cervical mucosa. One is inclined to believe that, in some of these cases, vicarious menstruation is set up. This is a very logical conclusion, when one considers that the genital canal, from the fimbriated end to the hymen, is developed from a common "anlage," yet it exhibits four variations of epithelium, and four widely different functions. And when we consider that the endosalpinx, endometrium and vagina respond to the menstrual cycle, it would be extraordinary did not the cervix show a similarly periodic change.

In one such interesting case, a woman at 42 first came under my observation. She had had a subtotal hysterectomy for fibroids, five years previously. For the past

year she had regularly periodic discharges of blood, simulating menstruation, every three weeks. She was an intelligent English woman, who said that the blood was unlike menstruation in that it came on and stopped more slowly than normal menstruation. She came fearing cancer. Nothing abnormal could be found on examination. Operation for other causes had to be done, and the stump was removed at the same time. It showed no trace of pathology. It is necessary but to mention the incidence of carcinoma in the stump of a subtotal hysterectomy. The assurance to a patient that cancer of the uterus is an impossibility after total hysterectomy is a comfort to the patient in which the surgeon rightly shares. Cancer of uterus is a constantly recurring fear in the emotional life of every woman of postmaturity.

It is not a matter of indifference whether one allows the ovaries to remain. With their removal, the incidence of late cervical pathology is greatly reduced; the incidence of immediate and intermediate postoperative hemorrhage is reduced, especially in vascular unstables; and the late return of bleeding from the stump is practically unknown after total removal of the ovaries, except in cases of newgrowth. There is not the slightest doubt that ovulation, estrin and progestin formation keep the tissues in the pelvis in a constant state of flux, with varying nutritional changes, rendering them much more susceptible to changes bordering upon, or invasive of, the domain of pathology.

My final plea is, if one's skill and experience warrant, if the case is a suitable one, a retrospect of cases shows that the total hysterectomy has much to commend it, above a subtotal. Where, on the other hand, the surgical risk, arising either in the surgeon or in the patient, would make the immediate risk the greater, then pursue the course that your conscience will dictate. But do not stop there, as regards the welfare of your prospective cases. Make yourself as proficient in the total as in the subtotal. It can be done. The mortality in this series is nil. The rest is in the lap of the gods.

TECHNIC OF TOTAL HYSTERECTOMY

The vagina is cleansed with sterile liquid green soap, and thoroughly dried. Care is exercised to empty the bladder completely.

Catgut, of the plain variety, chiefly Davis and Geck product, was used throughout. No. 2 was used for all major ligature purposes (never any larger size), and No. 1 for all peritoneal work. A minimum of catgut in each case was used. In over 90 per cent of cases, six No. 2 ligatures were sufficient. These were, ligation of the infundibulopelvic ligaments or the uteroovarian broad ligament, depending upon whether the appendages were to remain, or not. The next two ligatures are upon the lateral upturn of the uterine arteries, and the last two are upon the lower uterine branches, as far down as the fornices. The vault of the vagina is sutured continuously in two layers, with single No. 1, or No. 2, catgut as described later, and the peritoneum of the pelvic floor is united always by a single continuous No. 1 suture. Curved noncutting needles are used throughout, except when sewing the cervical stump in subtotal hysterectomy. I cannot overemphasize the importance of this little precaution. Round needles transfix. Cutting needles make a buttonhole and cause much unnecessary bleeding.

OPERATION

The abdomen having been opened, the patient is placed in an exaggerated Trendelenburg position. The intestines are then packed off, and the pelvis explored. In the uncomplicated cases, one determines at once whether the appendages are to be removed or not. If these are to be removed, they are held up by the hand of an assistant or by the operator, and the broad ligament "*clear space*" is located. This is a space below the ovary, bounded internally and outwardly by the uterine vessels. It consists merely of two layers of peritoneum, without any appreci-

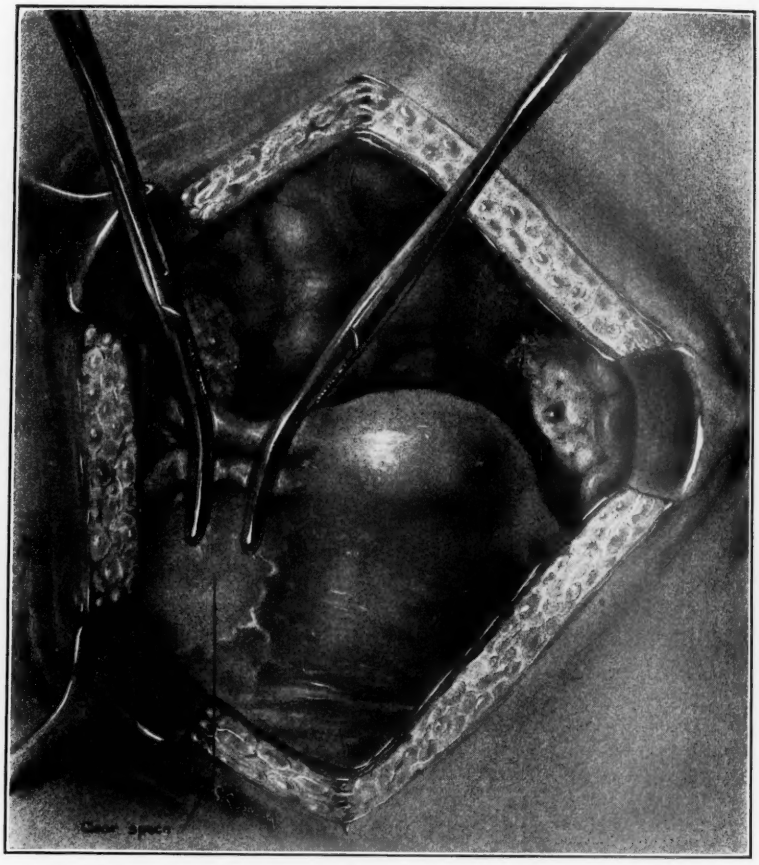

Fig. 1.

able tissues between them. If the finger impinges upon this area from behind, the digit will shine through anteriorly, or if the broad ligament is held up when tissues are lax, the space is translucent. A "Kelly" curved clamp (Fig. 1) is now placed upon the infundibulopelvic and round ligaments, having its tip in the clear space, and its convexity inward. A second and similar clamp is now placed upon the broad ligament between the ovary and uterus, with its tip juxtaposed to the tip of the first clamp. The appendages on that side are now completely isolated vascularly. In ordinary cases, the second clamp will include the proximal end of the tube, uteroovarian and round ligaments. This second clamp should be placed with its convexity outward. The appendages are now excised, being careful to leave at

least a quarter of an inch of tissue protruding through the forceps at the cut margin. This is to prevent slipping. The Kelly forceps should have longitudinal rugae along the whole blade, except at the tip, where they are corrugated, to prevent slipping.

The infundibulopelvic and round ligaments are now ligated by a figure of eight, which should transfix the round ligament, then through the "clear space," and again transfix the round ligament in the opposite direction. Ligation is then completed. The clamp should be released slowly as the ligature is tightened. I cannot

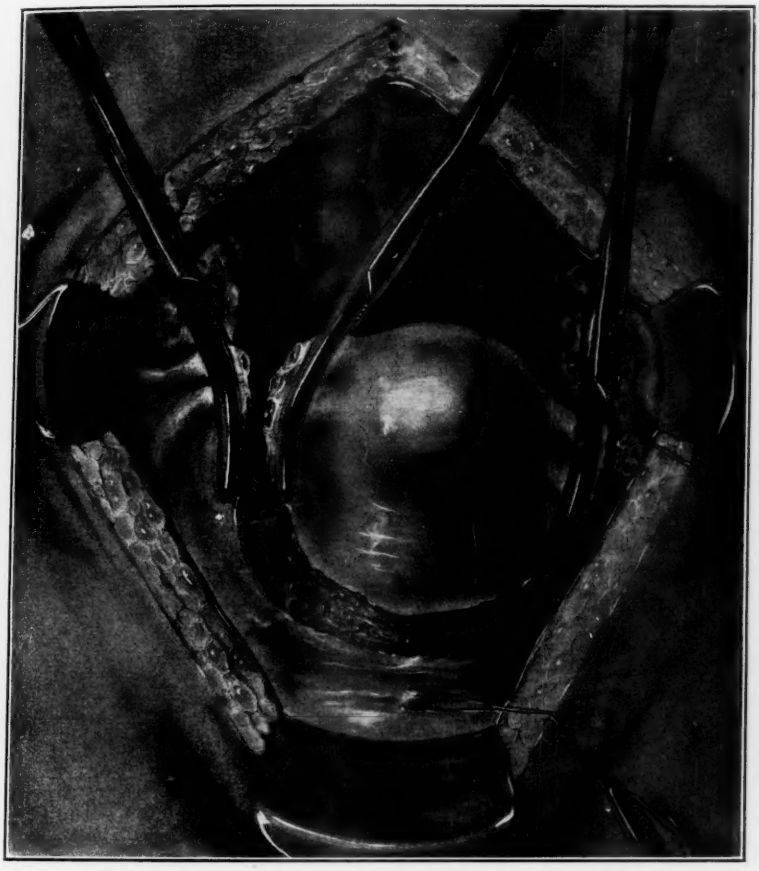

Fig. 2.

overemphasize the importance of this little procedure. Too quick release of the clamp, specially when dealing with the uterines, is inviting trouble, by allowing the tissues to escape from the grasp of the ligature.

The infundibulopelvic ligature is left long, and held by a forceps. On the opposite side the appendages are to remain. The "clear space" is again defined. The ovary and round ligament are pulled toward the pelvic wall and the first Kelly forceps is placed over the broad ligament, proximal to the ovary. Its tip should be in the center of the "clear space." Its convexity should be inward. A second is placed parallel to this, separated by one-third to one-half inch, with its convexity outward. These clamps include, in uncomplicated cases, tube, uteroovarian

and round ligament. Incision and ligation is now performed as described above, being careful to transfix the round ligament. There remain now but two Kelly clamps, which act as tractors upon the uterus. It is never necessary to grasp the uterus with volcella or any other form of tractor. These cause unnecessary loss of blood and tearing of tissue.

By its tractors the uterus is now pulled up and backward by the assistant, and the vesicouterine pouch exposed, by an anterior retractor. The anterior leaf of the peritoneum is now picked up on the left side at the vertex of the incision in the "clear space," and with a curved scissors, the peritoneum is incised in a curved

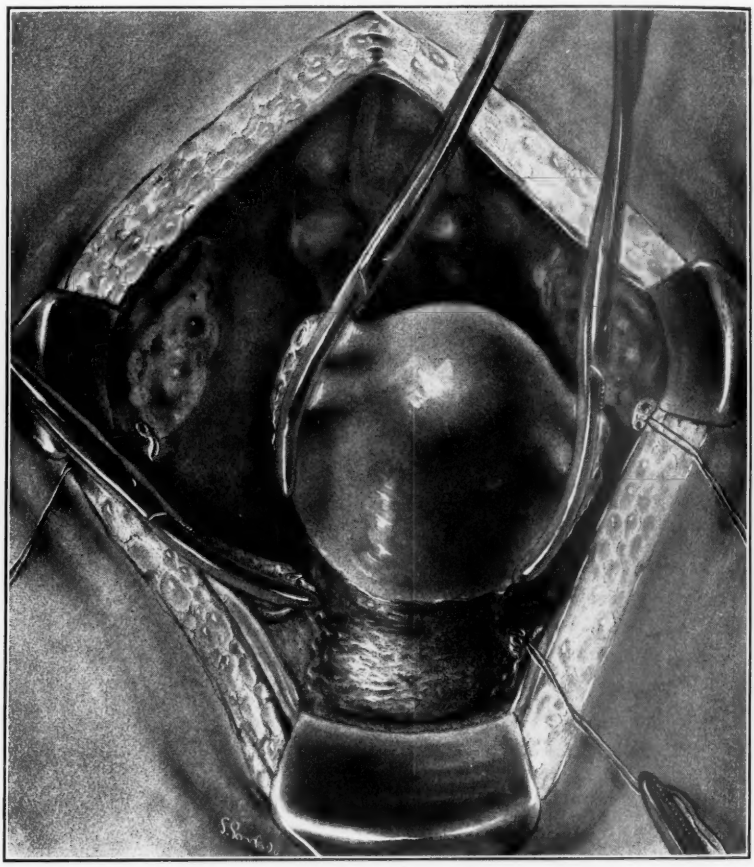

Fig. 3.

line in the vesicouterine peritoneal reflexion. The incision should end in the anterior leaf in the right "clear space." The operator now takes hold of the tractors with the left hand, and, with the index finger covered with one layer of sponge, the bladder is pushed down from the uterus and cervix. A No. 2 catgut now is made to transfix twice the bladder muscularis and vesical peritoneum (Fig. 2). This is not tied, merely held by an artery forceps. Traction is now put upon it by the second assistant, and a long special retractor measuring 2¾ by 4¾ is slipped below the reflected bladder, and the whole anterior wall of the uterus is now exposed. The uterus is again held by the operator and the separation of the bladder is now completed by the sponge-covered finger, down to the junction of the upper and middle

thirds of the vagina. An additional precaution lends a great deal of comfort. This consists in pushing the garnished finger well out on either side of the cervix and vagina, to separate the bladder from this region and to displace the ureters outwardly. A "Kocker" forceps with museux tip is now placed upon the upper uterine artery, at right angles to the uterine wall (Fig. 3). Its tip should impinge well into the uterine muscularis. Ordinarily it should be not less than ½ inch and not more than one inch above the portio. This can be easily determined by a finger of one hand in the anterior, and another finger posterior to the vagina. A similar clamp is placed on the opposite uterine at the same height. The artery is now cut ¼ inch from the clamp margin on both sides. In cases of large uterine tumors, it is neater to place on each side, a second similar clamp ½ inch above the first ones, to prevent a large escape of blood into the pelvic cavity. With a curved round needle the

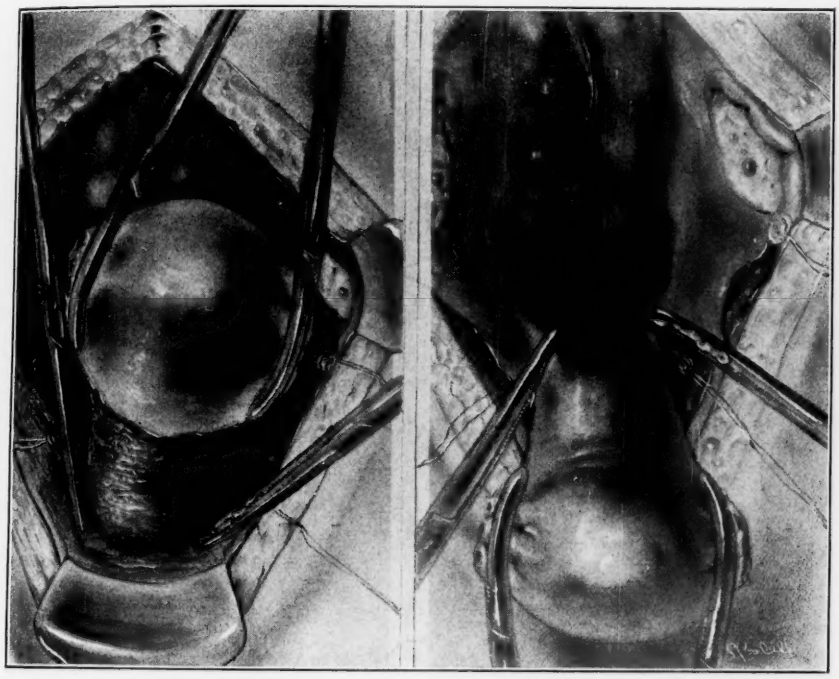

Fig. 4.

tissues are transfixed just below the forceps. The needle should not be driven through too close to the uterine wall, for reasons which will appear later. Ligation is now completed on both sides, and the clamps are removed.

The next step is securing the cervical branches of the uterines. Proceed as follows. First make sure that the bladder is clear, as above described, and held well out of the way of the cervix. Hemostasis should be complete. With the tractors pull the uterus up and out of the incision, and toward the symphysis, and expose the pouch of Douglas. Define the uterosacral ligaments (Fig. 4). Have your assistant pull the ligature on the upper uterine outward. Span the lower uterine with a "Kocker," placing the tip of the posterior blade mesial to the uterosacral of that side. Having made this impression posteriorly, turn your attention to the anterior blade. See that it is deep enough to go beyond the fornix. Then close it tightly on the cervix. Repeat the process on the opposite side. Care in placing these

clamps ensures safety to the ureters and bladder. The assistant now takes the handle of this forceps and draws outward and the operator cuts with a scissors boldly down the broad ligament, cutting always upon the cervix so as to leave one-fourth of an inch of tissue beyond the forceps on the cut side. The fact that you have reached the fornix is announced by a hollow sound quite different from that of the cervical tissues when severed by scissors. The process is repeated upon the other side of the cervix. When properly placed these last two straight clamps should converge at their points. The tissues uniting the lateral fornice to their broad ligaments are very loose and relatively bloodless, so that a portion of the lateral wall of the vagina can usually be freed, to equal that previously attained on the anterior wall. The assistant now holds the handle of the ''Kocker'' outward, the fornix of the vagina is now grasped with an ''Allis'' forceps on each side, the vagina is transfixed with a scalpel anteriorly, and the lower margin of the cut surface is caught with an Allis forceps. The circumcision of the vagina is now completed, above the two Allis forceps on the fornices (Fig. 5). The posterior vaginal wall is also grasped with a

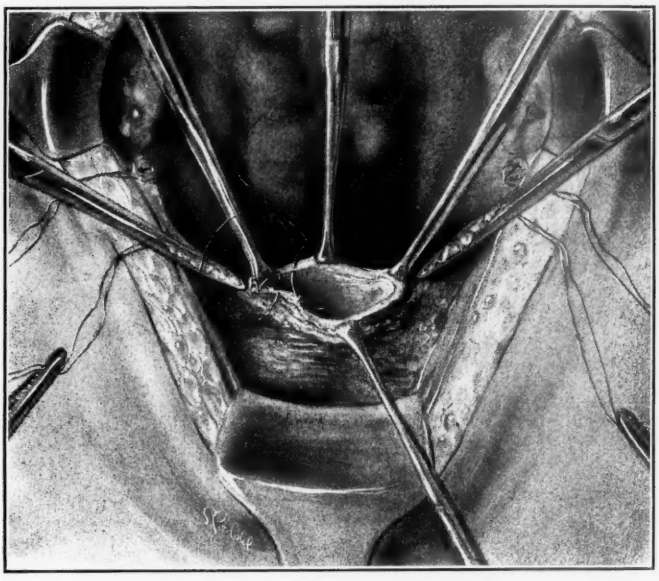

Fig. 5.

similar forceps. The vaginal vault is now defined by these four Allis forceps: one anterior, one posterior, two lateral. Any vessel in the paravaginal tissues (usually on the posterior wall) is caught within the grasp of an Allis. It is recommended that hemostat crushing forceps never be used where an Allis or other toothed non-crushing forceps will better serve the purpose.

It is never necessary to ligate the vaginal vessels. A continuous single No. 1 or No. 2 plain catgut (it should be long) is now used to close the vagina. One should begin at the patient's right, transfix from behind forward, and tie the first suture below and outside the Allis on the right lateral vault. The end should be held. Then continue across the vagina, being careful to close the left fornix completely. This suture should incorporate only the vaginal mucosa. Having reached the vicinity of the tip of the left Kocker, which still holds the lower uterines, the operator places a second layer over the vault, with the same continuous suture (Fig. 6). This should include posteriorly the intermediary tissues between the vaginal mucosa and peritoneum of the Douglas' pouch (including the latter, if so desired), and anteriorly

usually a well-defined cut layer of fascia between the base of the bladder and the vaginal wall. This is important in fixing the bladder from a sliding prolapse. The suturing should laterally stop short of the tips of the Kockers. The vault closure is now complete with the tying of the two ends of the continuous suture.

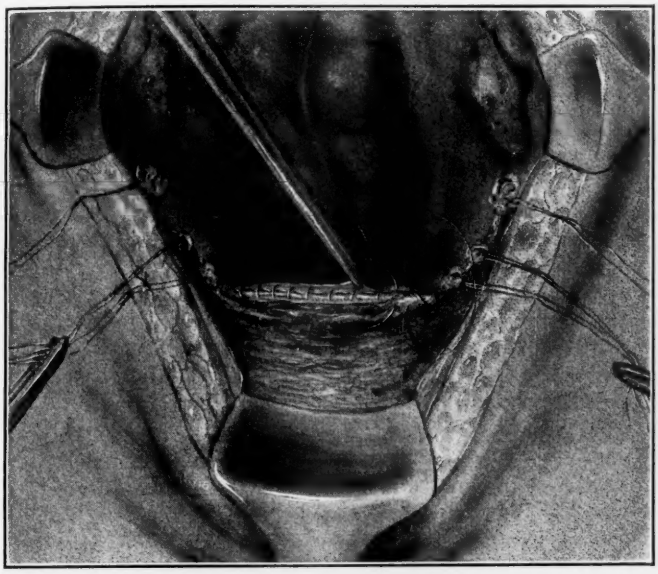

Fig. 6.

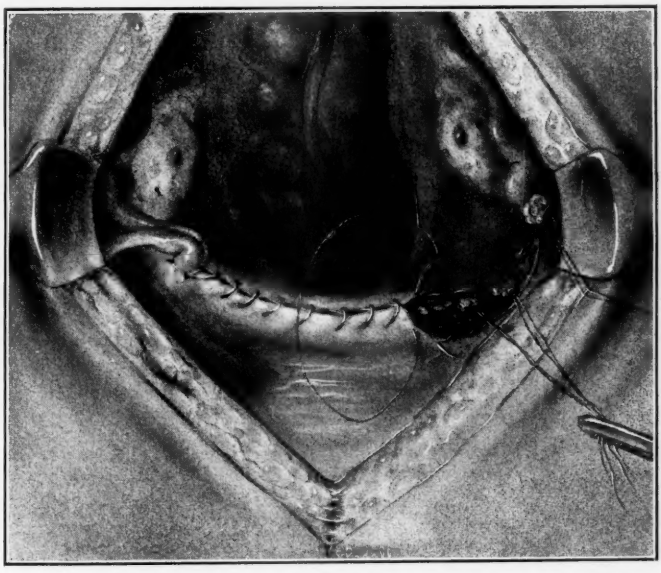

Fig. 7.

The lower uterines are now tied by transfixing the broad ligaments, just exterior to and slightly above the tip of the forceps, to insure that the ligature will remain distal to the forceps. The ligature is now looped and tightened down to the upper

margin of the tissue within the grasp of the forceps, as the handle of the Kocker is held toward the median line. The assistant now pulls the *handle* of the Kocker outward and the *tip* inward, and when so held, the operator tightens the suture, and, upon his dictum, the ligature is tightened synchronously as the assistant slowly releases the clamp. This ligature is inside the one previously placed upon the upper uterine. As a further precaution the ligature upon the lower uterines may now be tied over the ligature of the upper uterine ligature, in Staffordshire fashion. I have abandoned this method as unnecessary and productive of more knots for internal digestion.

Hemostasis should now be complete. The pelvic peritoneum is now closed as follows (Fig. 7). This is the most dangerous part of the operation. It is in this procedure that damage or ligation of the ureters most frequently occurs. I have catheterized the ureters in many cases, to demonstrate this. No. 1 single continuous is used. The posterior leaf of the clear space on the right is transfixed, then the suture is carried through the stump of the infundibulopelvic ligament (if appendages have been removed), or of the broad ligament (if appendages remain) internal to the primary ligature, and then it should pick up the layer of the anterior peritoneum beyond the round ligament. The assistant now pulls the ligature inwardly and one ties over the stump. The primary ligature and the single end of the continuous are now cut. One continues inwardly from right to left, closing posterior and anterior layers of peritoneum. As soon as one approaches the ligated uterines, one must proceed with greater caution. It is just here that the ureter emerges from among the uterine vessels and is covered only by a layer of peritoneum. Care should be taken that only peritoneum is included in the suture bite on the posterior wall. Once one has got past the right uterine ligature, one can proceed with impunity until the left uterine ligature is reached, where similar precaution is necessary. The left stump of the broad ligament or infundibulopelvic ligament is treated in a manner similar to the right. This line of suture draws the lateral supporting structures into a firm band of support in unison with the vaginal vault. The pelvic peritoneum has now been completely closed, and should be quite free from any exposed raw surface. Peritoneal toilet and closure of the abdominal wound complete the operation.

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Mankin, Z. W.: The Histogenesis of Endometriomata, Arch. f. Gynäk. **155**: 671, 1935.

The author believes that all endometriomas arise from bits of normal endometrium which through one or another mechanism become loosened and are reimplanted elsewhere. He does not feel that they can ever arise from bits of degenerating cells during menstruation. Normal endometrium leaves the uterus and becomes secondarily implanted in one of three ways: first, through the tubal lumen, second, by direct transplantation during operations and third, by way of the uterine lymphatics. The first method results in those endometriomas which are serosal in location and are found on other abdominal organs and on the parietal peritoneum. The second method results in endometriomas of the scars in the abdominal wall, and the third method produces those tumors which are found in the ovaries, the broad ligaments, etc. These tumors can become implanted only during the period between puberty and the menopause. The author believes that all other theories which have been advanced to explain the development of endometriomas must be discarded.

Ralph A. Reis.

TOTAL HYSTERECTOMY BY THE ABDOMINAL VERSUS THE VAGINAL ROUTE IN BENIGN UTERINE DISEASE*

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COMPLETE mastery of a satisfactory technic for total removal of the uterus by both the abdominal and the vaginal routes is a minimum standard of operative skill that every gynecologist should exact of himself as early in his career as the circumstances of his period of apprenticeship will permit. Otherwise he will find himself frequently confronted with situations in which the best interests of his patients cannot be served because of his lack of proficiency in executing the operation that is best adapted to their needs. For, unfortunately, neither of these operations is best suited to all individuals requiring hysterectomy, and superlative skill in the performance of only one of them becomes but an exhibition of poor surgical judgment and mediocre ability when applied to the correction of pathology that could be better treated by employment of the other.

But, thanks to the collective efforts of an illustrious group of pioneers in pelvic surgery, rugged foundations were long ago laid down upon sound surgical principles that have stood the test of time upon which successive craftsmen have ingeniously fashioned the fine superstructures of present-day hysterectomy technics, so that there is now available a sufficient number of perfected operative procedures for total removal of the uterus by both routes to satisfy even the most fastidious operator. Consequently, there no longer exists any legitimate excuse for failure to master at least one of each.

In a recent publication (Am. J. Surg. 28: 588, 1935), based upon a collective review of the literature on cervical stump cancer, I pointed out that subtotal hysterectomy is properly applicable to only four types of cases: (1) to those women requiring hysterectomy for benign disease who possess perfectly normal cervices; (2) to instances in which the operative hazard compels the execution of rapid and conservative surgery; (3) to a few cases where for good and sufficient reason it is of paramount importance to preserve the menstrual function; and (4) to most cases requiring hysterectomy during pregnancy. I also stated that because of the reprehensible prevalence of benign diseases of the uterine cervix, notwithstanding its many advantages, conservative subtotal hysterectomy has today only a limited field of application. Both in

*Also read by invitation before the Brooklyn Gynecological Society, Brooklyn, New York, December 6, 1935.

private practice and in clinic work it is the exception rather than the rule to encounter a normal cervix in conjunction with benign pathology of the uterine corpus requiring its ablation.

Now, if there is one fact more gratifyingly striking than the rest to be found in the recent literature upon total hysterectomy, it is that comparison of mortality statistics alone reveals practically no disparity between those who are wedded to the routine use of the abdominal operation and those who habitually employ the vaginal one. In both instances the immediate results obtained leave little to be desired and emphatically certify to the attainment of extraordinary surgical skill. But when a more inquisitive student undertakes to carry a comparison of results obtained with these two major operative procedures a bit further, he soon discovers that there is a woeful lack of recorded observations regarding the incidence of postoperative complications and duration of morbidity. And yet, certainly from the patient's point of view, such hazards as operative and postoperative hemorrhage, surgical shock, damage to bladder, ureters and rectum with consequent fistula formation, intestinal obstruction, cystitis, pelvic cellulitis, peritonitis, wound infections, phlebitis, thrombosis and embolism, pneumonia and the rest are realities to be specifically kept in mind while arriving at a decision as to which of the two operations under consideration offers the better guarantee of maximum success with minimum morbidity. For, let it be remembered that with the art of pelvic surgery so highly developed as it is today, there is scant ground for self-congratulation on the part of any gynecologist upon the mere attainment of a low operative mortality. The acid test of results obtained is applied through insistence upon unbiased follow-up observations continued not only during the period of hospitalization but also at intervals through later months, in order to determine the actual incidence of complications as well as the extent and duration of morbidity.

From such comparative studies one soon becomes impressed with the fact that in properly selected cases, a skillfully executed total hysterectomy by the vaginal route is a decidedly less formidable procedure as determined by its demonstrable effects upon the patient than is the same operation performed with equal finesse by the abdominal route. On the other hand, an attempt to broaden the scope of the vaginal operation beyond reasonable limits makes of it a mutilating procedure which serves only to discredit it and denotes neither sound judgment nor safe surgery. Obviously, it would be well-nigh impossible to lay down hard and fast rules that would infallibly govern one in the routine choice between these two plans of operative attack to which all pelvic surgeons would subscribe. Nevertheless, if at the outset of such an effort we fortify our contentions by setting up the premise that only those who have attained reasonable skill in the performance of both operations are qualified to offer constructive criticism, it should be possible to arrive at an agree-

ment both as to their relative merits and limitations. And so, with the hope of stimulating discussion that will ultimately achieve this end, I now venture to record certain convictions upon this subject arrived at only after deliberate contemplation of the teachings of others, coupled with and modified by my own observations and experience.

The following factors, it seems to me, are those that should govern the choice between the two operative methods:

1. *Age.*—Certainly no one will contest the assertion that major abdominal operations of any kind are not usually well borne by the aged and infirm. In this group abdominal panhysterectomy involves genuine hazard, whereas the vaginal removal of the uterus is astonishingly well tolerated. In middle-aged and younger individuals, while the difference is usually not quite as striking, there can be no question but that the immediate postoperative status of the average patient is distinctly better, the convalescence smoother, the incidence of minor complications diminished, and the period of morbidity shortened whenever the vaginal route can, with sound surgical judgment, be employed.

2. *Physical Status of the Patient.*—It cannot be too strongly emphasized that neither of these operations should be undertaken without a preliminary period of hospitalization sufficiently long to permit records to be made of a carefully taken history and complete physical examination, the latter to include, of course, such laboratory tests and other diagnostic aids as may be required to arrive at as accurate an estimate as possible of the individual's state of health and physical resources. Only strict adherence to this rule will safeguard the surgeon against the pitfalls of such surgical liabilities as obesity, severe grades of anemia, undernutrition, chronic exhaustion, and any one or more of a formidable list of constitutional and systemic diseases familiar to all of us. Discovery of the coexistence of any of these maladies with pelvic pathology that has prompted a patient to seek primarily the advice of a gynecologist imposes upon him the inescapable obligation to insist upon calling into consultation a competent medical colleague, in order that a comprehensive and intelligent plan of therapy may be evolved. Whereupon, it may appear that the contemplated pelvic operation had best be temporarily deferred or, perhaps, even abandoned altogether. If, however, it is deemed wise to include hysterectomy among the remedial measures agreed upon, it seems to me to admit of no argument that the restrictions thus imposed upon the surgeon compel him to employ the vaginal route whenever it is feasible to do so.

3. *Status of the Pelvic Floor and Supporting Structures.*—In nulliparous women whose intrapelvic ligamentous and fascial supports of the reproductive, vesical, and rectal units are normal and adequate, I always perform abdominal hysterectomy unless there exists some specific contraindication to its use. This, too, notwithstanding the fact that adequate

exposure for proper execution of the vaginal operation may always be had through use of liberal unilateral or bilateral Schuchardt's pararectal incisions. However, the bleeding from these incisions is always copious and reconstruction of the divided structures so as to avoid permanent and unsightly deformity of the vaginal introitus is not always achieved. Moreover, even with the additional exposure obtained by this means the hysterectomy may still be difficult and hazardous in women with deep pelves and strong, unyielding uterine supports. Complicated pelvic pathology, of course, tremendously increases the technical difficulties. Certainly, therefore, vaginal hysterectomy in the nullipara without uterine prolapse should be undertaken only by surgeons who have had large experience with this operation.

4. *Types of Pelvic Pathology to Be Dealt With.*—As a general rule, total hysterectomy by either route should not be undertaken if there exists acute or subacute infection anywhere within the boundaries of the operative field. The successful extension of present-day physical therapy to include even ambulatory dispensary patients is a commendable achievement, because it robs the time-honored argument which invokes the economic urge in justification of major pelvic surgery in the presence of active infection of most of its potency. There remains, nowadays, but scant excuse for subjecting any patient to this unnecessary surgical hazard. Someone has astutely suggested that if no elevation of temperature or of leucocyte count occurs following several vigorous bimanual examinations of the pelvic contents, one may safely conclude that the smouldering fires of lingering infection have become extinct.

Nevertheless, there often still remain, as the aftermath of the pelvic storm, extensive and dense adhesions involving not only the uterus and its adnexa but also the rectum, sigmoid, bladder, ureters, small bowel, and omentum. Usually, also, there is greatly diminished flexibility of the uterosacral and cardinal ligaments which offers strong resistance to downward traction applied to the cervix. Furthermore, the situation is likely to be complicated by the presence of cystic and adherent ovaries and bilateral hydrosalpinx. Under such circumstances I consider total hysterectomy by the abdominal route far preferable from every point of view.

Not uncommonly extensive pelvic endometriosis may closely simulate chronic pelvic inflammatory disease and cellulitis. A carefully taken history will often disclose a distinct and significant ebb and flow of regional pain intensity that coincides in a striking way with the several phases of the menstrual cycle reaching its maximum severity during the several days immediately preceding the flow. Moreover, such dysmenorrhea is frequently found to be of the acquired type, since the age incidence of this disease is predominantly after twenty-five. It is

commonly associated also with hyper- and polymenorrhea, although in many instances this is to be attributed to coexisting myomas or adenomyomas of the corpus uteri. Owing to the preponderance of endometrial implants at the bottom of the culdesac with subsequent extension to the anterior wall of the rectum and to the less common involvement of the bladder wall, symptoms referable to either of these organs and dominating the dysmenorrhea complex are particularly enlightening. In the last analysis, however, the diagnosis rests upon accurate interpretation of the findings upon vaginoabdominal and rectoabdominal palpation. There is a recognizable difference between cellulitis of infectious origin and infiltration occasioned by invading endometriosis, which is perceptible to anyone possessing a reasonably well-educated sense of touch. The difficulties of total hysterectomy may be greatly enhanced by extrauterine pelvic endometriosis. Each case must remain a law unto itself. In the majority of them I prefer the abdominal route, but if the major invasion has occurred in the rectovaginal septum, the vaginal route may offer worth-while advantages.

Again, when one encounters ovarian neoplasms in conjunction with the indications for total hysterectomy, it seems to me that both because of the vitally important matter of completing the ovariotomy without spilling any of the always uncertain contents of these tumors and because of the compelling indication in such cases to explore thoroughly the entire abdominal contents, laparotomy is obviously the route to be chosen. Preliminary evacuation of the contents of true neoplasms of the ovary is mentioned only to be condemned, except when the patient's condition compels its adoption as a last resort measure.

With regard to total hysterectomy for uncomplicated fibroid tumors associated with benign disease of the uterine cervix, several factors are to be considered before deciding upon the best method of operative attack. The most important of these are the size and the variety of the neoplasm. While it is unquestionably true that tumors as large, or even larger, than a four months' pregnancy may be successfully removed by the vaginal route, if morcellation is resorted to, the wiser course would seem to be employment of the abdominal route whenever the gross enlargement of the uterus exceeds in size an eight weeks' pregnancy. Caution should always be exercised in delivering through the detached vaginal vault even a tumor of this size because of the danger of serious damage to the base of the bladder and its sphincter muscle from overstretching. If intraligamentary, retroperitoneal, cervical, or subvesical fibromyomas are to be dealt with, one should always assume that normal anatomical relationships in the true pelvis have become distorted. Frequently this occurs to an extraordinary degree and failure to recognize the added operative hazards thus produced is responsible for many divided ureters and bladder punctures. In all such cases the abdominal route is obviously preferable. Nor should one

forget that pedunculated fibroid tumors of significant size are nearly always parasitic, obtaining much of their blood supply from adherent omentum, mesentery or gut, and that the separation of such adhesions even under direct vision through a laparotomy wound may be attended by considerable loss of blood. If there is no coexisting intrapelvic infection nor suspicion of malignancy in such cases, employment of the abdominal route permits use of autotransfusion throughout all stages of the operation preceding the final one of opening and detaching the vaginal vault. When one encounters extensive adnexal pathology complicating fibroid tumors, the abdominal route again is distinctly safer and easier of execution.

As pointed out under "Modification B" of my "Simplified Technique for Abdominal Panhysterectomy" published in 1929 (*Surg. Gynec. Obst.* 48: 248, 1929), if exposure of the cervix for the deeper dissection is rendered difficult by reason of the shape or size of a fibroid tumor, it is recommended that a subtotal hysterectomy at or above the level of the internal os first be done. Whereupon, the cervix may then be easily and speedily removed by use of the technic described. Obviously, this procedure should never be resorted to if there exists any suspicion of associated carcinoma of the cervical canal or of the corpus uteri. Fortunately, a preliminary diagnostic curettage affords an easy method for accurate determination of this question.

Total hysterectomy is frequently indicated in conjunction with the radical cure of various types of vaginal hernia, such as a large cystocele, rectocele, enterocele, and varying degrees of uterine prolapse, including complete procidentia. Some gynecologists advocate routine total hysterectomy as the preferential treatment of uterine prolapse and, until recently, I also subscribed to this view, basing my convictions upon the follow-up observations of private patients alone. However, in a recent statistical study of clinic cases operated upon in the Gynecological Department of the Johns Hopkins Hospital by a group of experienced men over a period of years, Everett (Surg. Gynec. Obst. 61: 403, 1935) found 30 per cent of recurrences after vaginal hysterectomy in prolapse cases as compared with only 4 per cent treated by the Watkins interposition operation. But whatever differences of opinion may exist regarding the best operative treatment of uterine prolapse, most gynecologists will agree, I think, that where total hysterectomy is indicated for other reasons in conjunction with correction of the various types of vaginal hernia, the lower approach is to be preferred.

5. *Association of Pelvic with Abdominal Disease.*—Only exceptional circumstances justify the performance of other major abdominal operations in conjunction with total hysterectomy. This is specifically true of elective gastrointestinal and biliary tract surgery. On the other hand, removal of a chronically involved vermiform appendix, or cure of an umbilical or ventural hernia may frequently be achieved in connec-

tion with abdominal hysterectomy and without added risk. Such procedures require, however, the exercise of sound and conservative surgical judgment.

6. *Associated Anorectal Pathology.*—Operative attack upon hemorrhoids, fissure and fistula-in-ano, rectovaginal fistula, and complete laceration of the perineum should not be combined with total hysterectomy by either route. If removal of the uterus must antedate correction of such maladies, my conviction is that subtotal hysterectomy by the abdominal route is far safer, because it evades the inherent danger of contaminating the operative field with subsequent development of serious, if not fatal, complications and also obviates the restrictions which such operations impose upon postoperative rectal therapy.

From this brief review of some of the major factors that should determine which of these two operations is best suited to the individual patient, it becomes evident that both of them have a wide range of usefulness and that under certain conditions each possesses distinct advantages over the other.

For the sake of emphasis, I have reserved for my concluding remarks a brief effort to focus attention upon one factor of safety common to both operations, the importance of which it would be difficult to exaggerate. Assuming that a preliminary critical and comprehensive diagnostic survey of the patient has wisely and judiciously accorded to the pelvic surgeon his proper place in the general therapeutic plan contemplated, and that the optimum time for the performance of total hysterectomy has been agreed upon between him and his medical colleague, this factor, perhaps more than any other, may determine the outcome of the operation as executed by either route both as regards mortality and morbidity. I refer to the degree of thoroughness with which the surgical toilet of the vulva, vagina, and cervix is carried out immediately preceding the operation. It is assumed, of course, that no surgeon would deliberately undertake a total hysterectomy by either route in the presence of any active infection of the vulva, Bartholin's glands, the urethra, the suburethral glands, or the cervix. But even in the absence of these obvious hazards, as many surgeons have learned from bitter experience, both the vaginal flora and the cervical glands may harbor the most virulent and dangerous types of streptococci, as well as other less formidable organisms. And there is abundant evidence to show that failure to recognize this fact is responsible for an occasional fatality and for many instances of postoperative wound infections, secondary hemorrhage, pelvic cellulitis, and other complications that contribute to a prolonged convalescence. Hence, the necessity for inflexible insistence not only upon extraordinary care being exercised in the surgical toilet employed but also that its application be delegated only to individuals sufficiently experienced to appreciate its importance.

9 East Chase Street

DISCUSSION ON PAPERS BY DRS. GOODALL AND RICHARDSON

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—We can agree with practically everything that Dr. Goodall has said without argument. Our technic is not identical with his, but this is not important, for after all it is the operator and not the method that counts.

The number of supracervical hysterectomies compared to totals in Dr. Goodall's series were about equal. There was a time in our clinic, under the leadership of the late Dr. Polak, when we did more total than subtotal hysterectomies. In later years, however, after developing what we think is a good technic for the supracervical operation, we are now performing practically all supracervical. For example, in the last five years at the Long Island College Hospital there were 327 supracervical operations, and only 11 total hysterectomies. We lost one patient in the 327 of the subtotal group and one in the 11 of the total group.

In our clinic at the Long Island College Hospital, we employ the following routine in supracervical hysterectomy: The night before operation we insert a light vaginal pack of 4 per cent mercurochrome. At the Methodist Episcopal Hospital we have used 4 per cent mercurochrome in over 16,000 obstetric cases and have reduced our morbidity from 12 per cent to less than 5 per cent and therefore we believe it to be a first-rate germicide. On the other hand, any germicide may be used. At operation we thoroughly cauterize the cervix through the vagina from the external to the internal os. In doing the hysterectomy we "core out" from above down to and past where we have cauterized from below, following which cauterization from *above* is done. These procedures leave a "shell of cervix" that does not produce leucorrhea or backache. Furthermore, the likelihood of subsequent malignancy is cut to a minimum, not so much as in complete hysterectomy, for naturally if there is no cervix there can be no development of carcinoma in it.

Goodall did not mention infection this evening, but he speaks of it in his paper, a low-grade infection, associated with hemorrhage. We have seen such a low-grade infection and believe it is a condition that we have to contend with, more particularly in total hysterectomy. With the use of a preoperative germicide in the vagina, we believe that the likelihood of infection is tremendously reduced.

In his paper Goodall also spoke of removing or leaving the ovaries with reference to the behavior of the stump of the cervix that is left. There is no doubt that with no estrin or progestin being thrown into the circulation, the tissues are not in the state of flux that they would otherwise be, and consequently it seems important to remove the ovaries whenever the patient is thirty-five years or more of age.

The final decision between supracervical and total hysterectomy cannot be settled. We should ask ourselves whether it is better to perform subtotal hysterectomy with its limited morbidity and mortality rate, but with the likelihood of continued leucorrhea and backache and a greater tendency to malignancy, or a total hysterectomy with no leucorrhea and backache and no fear of malignancy but with a greater primary morbidity and mortality. These questions, I believe, have to be left to the individual surgeon. Much depends on the condition of the patient and on the ability of the operator to perform the operation of his selection.

DR. SIDNEY A. CHALFANT, PITTSBURGH, PA.—It has been our practice also to do supravaginal hysterectomies as a routine, limiting the complete hysterectomies to the carcinoma cases and to an occasional case where the cervix is badly diseased.

Our technic in the supravaginal hysterectomy is thorough cauterization of the cervix, and if all of the endocervical mucosa has not been entirely destroyed from below, to complete that from above by coning out the cervix. The presence of fibroids with old infection of the pelvis makes the complete hysterectomy quite difficult, and we have never felt sure enough of our ability to do panhysterectomy in such cases.

One disadvantage in panhysterectomy that has come to my attention recently in two patients operated upon in other clinics was a very marked shortening of the vagina. Both of these women were comparatively young.

Our technic in complete hysterectomy differs a little from Dr. Goodall's. We usually circumcise the cervix from below with a cautery. The dissection between the uterus and the bladder is thus facilitated very much. We open the anterior vault of the vagina, turn the cervix up and clamp from the base of the broad ligament on either side. It gives us practically two ligatures on either side and obviates the difficulty that sometimes occurs from bleeding from the cut edge of the vaginal vault. Following cauterization we have met an occasional case of bleeding about the eighth or tenth day when the slough separates. This has never been serious.

To be able to report 550 consecutive hysterectomies without mortality shows surgical judgment and operative skill of the highest degree, but I believe the average surgeon who does the bulk of the hysterectomies of the country will have as a rule a satisfactory result and will have a lower operative mortality by doing a subtotal hysterectomy.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I have had considerably more trouble with complete abdominal hysterectomies in their postoperative recovery than I have had with the supravaginal operation. I cannot imagine what factors could come into play to produce a postoperative hemorrhage following a supravaginal hysterectomy after the eighth day, providing there has been no cauterization of the cervix.

I agree with Dr. Richardson entirely as to the indications which he has laid down for the supravaginal, total abdominal, and the vaginal hysterectomy. We differ only in regard to those cases where no strict indications exist for a particular type of operation. In such cases he prefers to take them out supravaginally while I take them out vaginally.

Since the last report I have done 68 additional vaginal hysterectomies, making 695 since the introduction of ethylene into the Presbyterian Hospital. There were no deaths in these 68 additional cases, making the record 3 deaths in 695. In the 695 cases there was one case of thrombophlebitis. In none of the cases did I tie off a ureter.

When one has developed his technic in vaginal hysterectomy according to the indications laid down by Richardson until he has reached the point where he is satisfied with it, he then should select a case a little more difficult each time. It occasionally happens that he must have this skill for a particular case. For instance, an extremely obese young woman may have uncontrollable menorrhagia where a laparotomy on account of her obesity would be too hazardous to consider, leaving vaginal hysterectomy as the only logical operation. If unable to do this operation, the surgeon then would resort to radium in a case where ovarian function should really be retained.

It does not require a Schuchardt's incision to remove the uterus vaginally in a nulliparous woman, and I have never yet made such an incision. At most a small perineotomy is needed. In these last 68 cases 21 were nulliparous women.

I would like to emphasize that occasionally the removal of the cervix by the vaginal route and the body by the abdominal route is advantageous, particularly if the cervix should be badly infected.

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—The choice between the vaginal and abdominal route in benign diseases of the uterus which requires total removal, is dependent upon several factors. First, the ease or the difficulty which the one or the other method affords in dealing with the diseased uterus, as well as the adnexal or intestinal pathology which may complicate the situation. No one can deny the superiority of the vaginal approach in the small myomatous uterus or in functional

bleeding when the vaginal outlet is sufficiently relaxed to permit of easy access to the field of operation. On the other hand, with a contracted vagina or with large tumors, abdominal hysterectomy can be performed more expeditiously; with less trauma to adjacent organs, less blood loss and more certain hemostasis. Certainly, the adequate exposure afforded by the abdominal route gives one more complete mastery of the situation in case inflammatory or neoplastic disease of the adnexa is encountered.

The second factor which must be considered is the mortality and morbidity incidence of each method. Reports by those particularly skilled in the performance of one or the other operation show a remarkably low mortality in both and what slight difference exists in the mortality rate is in favor of the vaginal method. As to the morbidity attending the two procedures, the absence of wound infection, the small incidence of phlebitis and lung complications make the immediate convalescence smoother in vaginal hysterectomy. I have seen no statistics dealing with the ultimate results, but from personal observation I have found no superiority of the one over the other.

Finally, the skill of the operator plays an extremely important rôle. I agree in principle with Richardson that the gynecologist should be equally skilled in both methods, but the truth of the matter is that in practice this does not apply to many of us. Had I the skill of Sproat Heaney in the performance of vaginal hysterectomy, I, too, would be its ardent advocate; lacking this, I shall continue to favor the total hysterectomy of Richardson which has given excellent results. I represent a clinic in which vaginal hysterectomy has never been a popular procedure, and we can be criticized justly for not using it more frequently. However, extending the indications for the vaginal approach to include lesions which can be handled more satisfactorily by the abdominal route is also to be criticized.

DR. JAMES C. MASSON, ROCHESTER, MINN.—We must realize that there is a legitimate field for the three types of operation and definite special indications for each one of them. I am satisfied that any gynecologist who is doing much surgery can do any one of these operations with almost an equal mortality and morbidity.

The ordinary surgeon who is not specializing in pelvic diseases is inclinded to overlook the value of vaginal hysterectomies, especially in cases of slight prolapse associated with a cystocele. In spite of what one of the essayists said, I believe the cystocele can be more satisfactorily taken care of by the vaginal route.

I feel that the subtotal operation should be done in young women who are still in the active menstrual period. It is important to save some of the cervix, and in some cases it is advisable also to save some of the endometrium above the internal os. In the great majority of cases, in women at the menopause or later, especially if they have had children, the total operation is the one of choice and in the hands of any one who is doing much pelvic surgery it can be done as safely and with less morbidity than the incomplete operation.

Our statistical department has given me some statistics on these operations, covering ten years from 1925 to 1934 inclusive. There were 2,085 total hysterectomies for benign conditions, with a mortality of 1.5 per cent. There were 2,002 subtotal hysterectomies for benign conditions, with a mortality of 1.4 per cent. There were 834 vaginal hysterectomies for benign conditions with a mortality of 1.7 per cent. The vaginal hysterectomies were done, I must admit, on bad surgical risks, many being elderly and many stout people. I do not think, however, that the stoutness alone should interfere with the abdominal operation if the patient is in good surgical condition. These patients seem to stand the operation very well if it is not too prolonged.

In regard to removal of the cervix and the danger of cancer, I do not feel that the cervix that is left has any increased danger of becoming malignant, yet in the

clinic where I work we have seen more than 100 cases of epithelioma of the cervix. There have been over 500 cases altogether that came to the clinic complaining of some trouble in the cervix following subtotal abdominal hysterectomy, the great majority of them having had no trouble in the cervix before operation. In about half of these cases there was enough trouble so that it was thought advisable to remove the cervix. These are the combined results of eleven operators.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—After reading in the preliminary report of this meeting the titles of the two last papers, I looked up the records in the Woman's Hospital for hysterectomies done in the past twenty years.

YEAR	VAGINAL	SUPRAVAGINAL	COMPLETE
1916-1925	321	2,267	619 (Incl. Wertheims operation)
1926-1930	152	1,218	255
1931-1935	245	1,217	398
Total	718—2.7 %	4,702—3.04%	1,272—4.24%
Grand total	6,692—3.23%		(Without Wertheims, 3.3%)

The above table shows the mortality for all hysterectomies done by the attending staff including those done by the internes in the Woman's Hospital in the years from Jan. 1, 1916, to Dec. 31, 1935. There were several Wertheim operations in the total hysterectomies, and if we deduct these deaths, the mortality for the total hysterectomies is 3.3 per cent or a difference of only 0.3 per cent from the subtotal hysterectomies.

I am heartily in accord with Dr. Richardson in the limitations for the proper use of total hysterectomy, but I do believe that suitable cases can be operated upon by total hysterectomy by those specializing in pelvic surgery, who are willing to study the anatomy and technic, with as low a mortality as in the subtotal operation, or with even a lower mortality for it is certainly safer to remove the whole of a diseased organ than to cut into it and then leave a large portion in situ.

I have been interested to follow the admirable work that the American Board of Obstetrics and Gynecology is doing to develop young applicants. I only hope that they will include more anatomy in their requirements. I do not wish to minimize the importance of pathology, but it is seldom that the opinion of an expert pathologist is needed in a major operation, and a knowledge of pelvic anatomy is absolutely necessary at every step of an operation. I hope, too, that the time will come when the Board will be given the authority to supervise or lay down a course of instruction for internes who are specializing in obstetrics and gynecology, with instruction in anatomy and in technic, and perhaps to appoint someone to pass on the ability of an interne to use his hands before he has gone too far in the curriculum.

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—During the past few years in our service there have been about 550 abdominal hysterectomies, the majority of which have been done supravaginally. In this series there were two deaths, one of which was due to anesthesia. During the past four years we have used vaginal hysterectomy more liberally and in that length of time 170 cases have been done with no deaths. When we first began the frequent use of this operation we had two postoperative hemorrhages, neither of which was serious and both of which were easily controlled. In the last 100 cases no bleeding has occurred.

We do not use vaginal hysterectomy for the removal of large tumors or in dealing with cases in which pelvic inflammation has occurred or where extensive postoperative adhesions are feared. It seems appropriate that the gynecologist should use either method of approach and that he should be able to fit the operation to the patient.

In the hands of the average operator the mortality as shown by John G. Clark some years ago was about 5 per cent, far higher than that which is attained by expert pelvic surgeons, and the difference in the mortality of the two operations in average hands is probably greater, although there is little or no difference in the hands of the expert. In the average hands, therefore, subtotal operation is probably safest.

DR. JOHN A. McGLINN, PHILADELPHIA, PA.—In our last 100 cases there were 14 vaginal hysterectomies, by ligature, 9 vaginal hysterectomies by clamp, 3 total abdominal hysterectomies, and 74 subtotal abdominal hysterectomies. One of my group is to report, in the fall, 250 vaginal hysterectomies without a death.

We are very much the victims of our ancestors, and Philadelphia surgeons have never particularly favored the vaginal operation. It is only comparatively recently that I have done a vaginal hysterectomy in a way satisfactory to myself. But now that I am able to do all types of the operation I feel that I can select the operation which best fits the individual case.

Now do not let anybody criticize the vaginal hysterectomy with clamps on any academic basis unless they have had actual experience with the operation and have followed the convalescence of the patient for a year or two. I might say that since adopting vaginal hysterectomy with clamps we are operating upon women of forty years with endocrine bleeding, where we formerly used radium.

DR. GOODALL (closing).—I purposely did not deal with vaginal hysterectomy because this paper was a discussion between abdominal total and subtotal. The number of vaginal hysterectomies that I have done, I cannot give offhand, but they constitute quite a small percentage of the total hysterectomies done in the various hospitals.

RETROPERITONEAL PELVIC TUMORS ENCOUNTERED BY THE GYNECOLOGIST

JAMES RAGLAN MILLER, M.D., HARTFORD, CONN.

GYNECOLOGISTS from time to time are faced with the problem of differential diagnosis of a mass lying behind the peritoneum either in the true pelvis or in such proximity to the pelvic brim as to suggest its origin in the genital organs. Discussion in this paper is limited to nongenital tumefactions, lying behind the posterior peritoneum in and about the pelvis.

While it is usually possible before operation to reach a definite conclusion as to the retroperitoneal location of a tumor, only too often the exact nature and location are first disclosed after opening the abdomen in the course of a procedure which the operator thought to be a simple gynecologic maneuver.

It is possible also in most cases when the abdomen is open to make an accurate diagnosis by gross inspection or when in doubt to obtain a frozen section for immediate microscopic diagnosis. There are, however, certain masses which may not be biopsied without seriously impairing the patient's chances for ultimate and even for immediate recovery.

Such problems come but rarely even to the surgeon of large experience. When he meets the situation successfully, he is not likely to report the case unless it presents some unusual features such as enormous size, and if the patient does not survive, he is even less inclined to mention it. Many highly instructive lesions are thus lost from view, whereas much might be learned if they were properly classified and made available for study as a regional problem. One gains the impression on reading the literature that chapters in the various systems have been based largely on the reports of single types of cases viewed from the pathologic and not the regional point of view. Only in the systems of surgery and in the textbooks of pathology is the region, as such, considered.

The purpose of this paper is, therefore, to fix attention on the various possibilities which the narrowly trained specialist may encounter to his own discomfiture. The case histories here reported are partly my own and partly those which have been made available by my associates.

1. URINARY TRACT

Anomalies of the upper urinary tract recently reviewed by Gutierrez[1] are usually suspected and diagnosed by well-known pyelographic methods. Silent lesions of the urinary tract, however, may be encountered during operation for fibroid uterus or tumor of the ovary. The possibility of solitary kidney must be borne in mind, also the fact that ectopic kidneys do not, merely because of their position, require treatment. If removal is necessary, one must remember that the blood supply of anomalous organs is usually anomalous. Thomas and Barton[2] state that abortions are caused by pelvic kidneys which are often mistaken for ovarian cysts, and they point also to the danger to mother and baby in full-term pregnancies.

Frank[3] reported a patient (Case 3), aged thirty-five years, who had 2 deliveries and 19 spontaneous abortions, presenting a globular mass deep in the left posterior pelvis which felt to him like the lower pole of a kidney. Diagnosis was confirmed by pyelography and proved by operation which was done for other reasons. The kidney was found to be cystic but was not removed. Any lesion which may occur in the normally placed kidney may be found in the ectopic pelvic kidney. An example of such a puzzling urinary tract condition is the following:

CASE 1.—H. H. (No. 300215.) (Courtesy Dr. T. N. Hepburn.) Female, aged twenty-nine years, complaining of incontinence of urine since operation at age of six, at which a supposed abscess of the left ovary was drained both abdominally and vaginally. A urinary fistula into the vagina resulted which resisted several attempts at closure. This patient proved to have a third rudimentary kidney located as usual above the normal kidney on the left and emptying into the vestibule, as indicated by vestigial remains of its ureter. The original operation was, in fact, a drainage of an infected hydroureter, and the patient was ultimately cured by an extensive resection of the anomalous third urinary tract.

Ectopic pelvic kidneys have been very rarely observed in the Hartford Hospital in female patients. One personal instance is as follows:

CASE 2.—H. H. (No. 311669.) Patient, aged twenty-eight years, came to operation for endometriosis of the ovaries. Before operation, an ectopic kidney on the left was thought to be a retroperitoneal fibroma. Pyelographic study confirmed

by operation showed this to be an ectopic left kidney just above the pelvic brim, rotated 180 degrees on its vertical axis, so that its pelvis lay to the left and the cortex to the right. The kidney functioned normally and was not disturbed.

2. TUMORS OF BONE AND CARTILAGE ARISING FROM THE LUMBOSACRAL VERTEBRAS AND PELVIC BONES

Osteochondromas and similar tumors, both benign and malignant, are usually so hard to palpation that x-ray study is obviously called for and leads to diagnosis and treatment in conjunction with an orthopedic surgeon. According to Ewing,[4] the most common tumors in this region are giant cell tumors, multiple myelomas, and osteogenic periosteal sarcomas.

3. INFECTIONS OF THE RETROPERITONEAL SPACE

CASE 3.—H. H. (No. 198290.) (Courtesy Dr. A. M. Rowley.) Female, aged twenty-nine years. When asked to see this patient twelve hours before her death and while she was under an anesthetic, I found a large boggy mass in the pelvis behind the rectum, displacing it to the right. Under guidance of fingers in the vagina and rectum, I punctured the mass through the left vaginal fornix, evacuating a large amount of thick yellow odorless pus which showed *Staphylococcus aureus* on culture. The history of this patient showed an increasing fever for fourteen days with inability to walk. On the second day of her illness her physician treated her for pelvic inflammatory disease. Seven days before death she showed motor and slight sensory disturbances of the lower extremities, high white blood count and high cell count in the spinal fluid, increasing incontinence of urine, a positive blood culture of *Staphylococcus aureus,* and a urine which contained *B. coli* and a nonhemolytic streptococci. X-rays showed no evidence of osteomyelitis. Autopsy revealed a *Staphylococcus aureus* abscess 15 by 10 by 10 cm. in the hollow of the sacrum behind the rectum, which had dissected the large nerve trunks of the sacral plexus. It could be traced to within 2 cm. of a healed furuncle on the left buttock about 5 cm. behind and to the side of the anus. Autopsy revealed also an operative puncture wound in the deep culdesac of Douglas from which a general peritonitis could have developed. Though the outcome in this case was not altered, it clearly indicates the ideal approach to such masses is posteriorly to one side of the tip of the sacrum or even directly through the rectum.

CASE 4.—H. H. (No. A 739.) Osteomyelitis of the fifth lumbar vertebral body. (Courtesy Dr. O. R. Witter.) I was asked to make a pelvic examination on an unmarried woman, twenty-four years of age, four days after onset of acute left lumbar pain with fever. The pelvic organs were normal. There was a great tenderness at the lower end of the left sacroiliac joint by rectal touch, and I suggested suppuration of this joint cavity as a possibility. Three days later at autopsy, a retroperitoneal bulging mass was found over the left posterior pelvic wall covering the sacroiliac synchondrosis. Ten cubic centimeters of thick green *Staphylococcus aureus* pus was obtained, originating from many areas of osteomyelitis in the body of the fifth lumbar vertebrae. The pus had burrowed through the obturator foramen toward the head of the femur and beneath the gluteus muscles. Generalized sepsis was present with abscesses in the lungs and kidneys.

4. EARLY PSOAS ABSCESS

No case of early psoas abscess was encountered by the Gynecological Service in the Hartford Hospital in recent years, and it is not likely that serious errors would arise, for if the abdomen were entered for correction of other serious pelvic conditions, as in the case reported by Frank,[3] the location of the mass behind

the iliac vessels would indicate the nature of the lesion. As in Frank's case, such masses must not be aspirated and the patient should be placed under appropriate orthopedic care. It is to be hoped that the possibility of psoas abscesses will not be beyond the mental horizon of the gynecologist who may happen on such a rare case in these days of narrowed specialism and diminished incidence of tuberculosis.

In one case on the general Surgical Service at the Hartford Hospital, an unrecognized psoas abscess was inadvertently drained at laparotomy. The patient survived but a sinus tract has persisted.

5. CHRONIC ILIAC ADENITIS

Frank[3] also reported a case of massive adenitis of the iliac glands secondary to an inflammatory focus of the lower extremity. Differential diagnosis in this case included malignant thrombosis of the external iliac veins, osteosarcoma of the left pubic bone and carcinoma of the ovary. Exploratory operation disclosed a large conglomeration of swollen lymphatic glands along the course of the external iliac vessels. An inguinal gland on biopsy showed nonspecific inflammatory hyperplasia with reticular cell proliferation.

6. EMBRYOLOGIC CYSTIC REMAINS OF THE WOLFFIAN BODY

CASE 5.—H. H. (No. 284439.) (Courtesy Dr. E. R. Lampson.) Female, aged forty-one years, para ix. Had been well since cholecystectomy three years previously. She suffered from needle-like pains in the right flank for four to five months, increasing in severity. A mass the size of a hen's egg high in the right groin was at first taken to be a hydroureter, but x-ray study showed it to be independent of the urinary tract and lateral to the cecum. This proved to be a cyst 7 cm. in diameter, lined by a single layer of flattened cuboidal epithelium, and was easily removed.

7. RECURRING RETROPERITONEAL FIBROMYOMAS

CASE 6.—H. H. (No. 312699.) (Courtesy Dr. A. M. Rowley.) Female, single, aged fifty-two. At age forty-three, the uterus had been removed above the cervix for fibromyomas which were shown to be of the usual variety. On her second admission eight years later, a tumor 16 by 3 by 9 cm. was removed from the upper abdominal retroperitoneal tissue behind the small bowel and its mesentery. At her third admission four months later, several more tumors were removed from the same location, the largest of which was 12 cm. in diameter. At her fourth admission four months later, she complained of low back pain extending down her right thigh and a bearing-down sensation in the lower abdomen. Several large tumors were removed from the retroperitoneal tissues behind the small bowel, the largest of which was 20 cm. in diameter, and one of the smaller tumors was removed with great difficulty from its location adjacent to the aorta. Careful review of all the slides failed to show any nerve tissue or evidence of malignancy. Careful search of all the retroperitoneal tissue was made at the last operation and no further nodules were found.

Within four months after the patient's previous operation, she again presented herself with a rapidly growing tumor of the same general description and location. In addition, this time she had a tumor 4 or 5 cm. in diameter in the upper end of the biceps muscle which had grown within the last three to four months. Further operative treatment is contemplated and will be reported later.*

*Six months after previous operation, numerous similar fibroids were removed at laparotomy from the retroperitoneal tissues to the right and behind the ascending colon. The cellular structure showed no anaplasia and Masson's stain shows no nerve elements. The mass in the biceps muscle disappeared spontaneously.

8. RETROPERITONEAL LIPOMAS

Numerous reviews of these interesting tumors emphasize not only the tendency to sarcomatous degeneration but also the great danger of very large tumors due to injuries of the blood vessels and of the bowel. Mechanical difficulties at times may be insurmountable even for the most skillful surgeon. These tumors are often mistaken for large ovarian cysts.

CASE 7.—H. H. (No. 179996.) (Courtesy Dr. C. H. Elliott.) The patient aged forty-two years, nullipara. This patient was admitted with the diagnosis of cystadenoma of the ovary, probably malignant. She had been operated upon for fistula in ano elsewhere four years previously, but as she weighed nearly 260 pounds at that time, her surgeon can be excused for making no note of an abdominal tumor. During the past three years she has lost 70 pounds and only recently noticed an abdominal mass. The menses were normal. The upper abdomen appeared to be filled by a solid tumor which, however, gave a highly suggestive fluid wave. The diaphragm was pushed high and the uterus was pushed forward by a semisolid feeling mass in the pelvis which seemed to be continuous with the upper abdominal tumor. X-ray examination showed the viscera displaced to the left. At operation numerous retroperitoneal lipomas were encountered, all of which could not be removed. Four separate masses totaling 6,000 gm. were removed, but several masses in front of the left kidney and below the pelvic brim had to be left. A fecal fistula developed, and in a desperate attempt to close the fistula three months later, because of progressive weakness and vomiting, the patient died. Autopsy revealed a putrid peritonitis which involved both the peritoneal cavity and the remaining lipomas and retroperitoneal tissues. The tumors which remained weighed 5,800 gm.

Retroperitoneal lipomas usually extend within the confines of the abdominal cavity, but the case reported by Deupert[5] indicates that these tumors may seek room for extension outside the pelvic cavity by way of the pelvic foramina. He found a huge lipoma with sarcomatous degeneration emerging through the obturator foramen from within the pelvis. He removed the intrapelvic portion by morcellation through the obturator foramen under guidance of laparotomy. The patient survived the immediate operation but shortly developed a recurrence.

9. RETROPERITONEAL NEUROLIPOMA

In spite of the general opinion that such cases as the two previous ones owe their origin in part to nerve tissue, no histologic proof of this could be shown. The following case, however, was such an example. (Personal case—patient operated upon at St. Francis Hospital.)

CASE 8.—Patient, aged thirty-four years, whose chief complaint was sterility of five years' duration. Shortly after her marriage, a fibroid tumor was diagnosed and observed for two years without growth. I found an anteflexed, small fibroid uterus, and in addition a firm tumor mass filling the entire hollow of the sacrum and extending well above the pelvic brim in front of the promontory. X-ray showed no evidence of osteochondroma. At operation three small fibroids were enucleated from the fundus and a retroperitoneal tumor was found covering almost the entire surface of the sacrum, extending 3 to 4 cm. above its pelvic brim. The right ureter coursed over its right edge for a distance of 10 cm. The tumor was removed through a long midline peritoneal incision mostly by sharp dissection, for numerous sympathetic nerve fibers bound down the mass in a manner which reminded one of the restraint under which Gulliver was placed by the Lilliputians. The internal iliac vessels on both sides were laid bare with difficulty, and one branch of a large vein deep in the pelvis was injured, causing considerable bleeding. This was

ligated, a transfusion was given, and uneventful recovery ensued. Pathologic examination showed a neurolipoma about the size and shape of a plump full-term placenta.

10. BENIGN TUMORS OF THE PERIPHERAL AND AUTONOMIC NERVOUS SYSTEM

Whether the previous case arose from, or was complicated by, nerve tissue, numerous examples are found of true nerve tissue tumors such as the following:

CASE 9.—H. H. (No. 294395), single, aged forty, suffering from gradually advancing multiple sclerosis of five years' duration. The presenting symptoms were urinary urgency and frequency of voiding. Examination showed a cystic feeling tumor occupying the left half of the pelvis and displacing the normal uterus to the right. Operation was done under a diagnosis of ovarian cyst and disclosed a bright red, cellular tumor, 12 by 9 by 9 cm., lying retroperitoneally two-thirds below and one-third above the pelvic inlet and to the left and behind the sigmoid. Removal was accomplished without great difficulty by sharp dissection of the many thread-like nerve filaments which bound the tumor to the lateral pelvic and sacral walls. The blood supply of the bowel was not injured, and the patient has remained well for two years. Microscopic examination showed a very cellular neurofibroma with fasciculi of cylindrical and fusiform cells which are uniform in size and stain and which show no anaplasia and only a few regularly formed mitoses. A few areas of myxomatous degeneration were noted.

CASE 10.—Tumors of the nerve sheath, so well summarized by A. P. Stout,[6] have not been demonstrated beyond question in our experience. The following case, however, is very suggestive and presented a picture similar to that reported by R. T. Frank[7] under the name of schwanoma.

H. H. (284966), aged thirty-seven years, para i. The presenting symptom was pain in the right sacroiliac region, radiating down the right leg and into the perineum which had been developing since a very difficult high forceps delivery eleven years previously, followed by a febrile puerperium. She stated that her anesthesia had been incomplete and she remembered the pain down the leg at the time of the forceps delivery. Extensive urologic, orthopedic, and neurologic advice had been sought under excellent circumstances. Prominent gynecologists had advised removal of the tube and ovary on this side. I could find no abnormality of the adnexa, but movement of the cervix forward and away from the right side caused pain. Just above the right ischial spine in the region of the sacral plexus, there was a distinct cystic feeling mass 1 by 2 by 4 cm., pressure on which made the patient cry out with pain identical with her chief complaint. There were no neurologic symptoms in the distribution of the right sacral plexus and proof of the nature of this tumor could not be obtained since she refused operation. I believe, however, that this may well have been neurilemoma or schwanoma of traumatic origin.

11. RETROPERITONEAL MYOSARCOMA

CASE 11.—H. H. (No. 310917.) (Courtesy Dr. G. H. Howe.) Patient aged fifty-eight years, para ii. Patient entered with a history of enlarging abdominal mass during the past three to four months, nausea and vomiting, loss of weight and strength, and sharp attacks of pain in the left upper quadrant and epigastrium. Twenty years previously one ovary and part of the other were removed together with the appendix. Her abdomen was enlarged to the size of an eight months' pregnancy by a firm mass which was dull to percussion. Under diagnosis of carcinoma of the ovary the abdomen was opened, disclosing a large amount of amber colored fluid and papillary implantations throughout the peritoneum with metastatic involvement of the omentum and intestines. A cystic mass the size of a large orange

arose from the region of the right ovary. A large specimen of omental tissue was removed, and the patient died on the sixth day from a secondary hemorrhage. The essential findings at autopsy were a tumor mass lying lateral to the ascending colon retroperitoneally, associated with a cyst about 10 cm. in diameter which had a thick fibrous wall. There was no connection with the genital organs. Metastases were found in the adrenal, the seventh rib and throughout the peritoneum.

Microscopic study showed a highly malignant tumor of large multinucleated cells with slightly eosinophilic cytoplasm. The cells were fusiform in shape with many fibrillary extensions. Some cells were small and round. The cecum was infiltrated by the tumor only as far as the mucous membrane. In view of the multinucleated and irregular mitoses, the fascicular arrangement and fibrillary structure, our pathologists leaned toward diagnosis of a malignant neurogenic tumor, possibly a glioma, but further study, in which Dr. James Ewing concurs, led to a diagnosis of myosarcoma.

12. RETROPERITONEAL SARCOMA

Many reviews in the literature point to the relative frequency of sarcoma of the retroperitoneal connective tissues, either as primary growths or as sarcomatous degeneration of tumors which are otherwise benign.

CASE 12.—H. H. (No. 287880), aged thirty-four years, gravida iii, para ii. Her last pregnancy was an abortion one year previously. On admission this patient was again in the third month of pregnancy. Her uterus was pushed high to the left by a retroperitoneal mass projecting into the right pelvis and reaching as high as the right iliac fossa behind the cecum. This tumor was hard and smooth, the size and shape of a flattened grapefruit. Another small tumor was noted at its upper pole. At operation the ureter was plainly visible in front of the mass. The uterus was emptied by hysterotomy with ligation of the tubes. A biopsy was taken which showed distinctly anaplastic groups of round cells with an indefinite intercellular supporting stroma. The nuclei were round and deeply staining with a diffuse chromatin structure. Diagnosis was made of retroperitoneal sarcoma of mesoblastic origin. Subsequently this patient received intensive deep x-ray therapy which apparently retarded the growth until her death occurred four and a half years after operation. The nerve supply of the right leg was seriously involved even from the first.

CASE 13.—H. H. (No. 258070), aged sixty-five years, single. On her first admission, radium and x-ray therapy were given for papillary adenocarcinoma of the fundus (Grade 3, Healy). Five weeks later panhysterectomy was done and no extension of the growth was observed. Four months later a thickening of the left parametrial tissue was observed, and on x-ray study a retrorectal mass 10 cm. in diameter was diagnosed as a recurrence of the uterine carcinoma and further x-ray radiation was given over the pelvic region. No improvement occurred and a biopsy of the growth was obtained at exploratory laparotomy from a soft retroperitoneal mass behind and to the left of the sigmoid and rectum. Microscopic study showed a very cellular malignant tissue, consisting of moderately large cells containing large, oval or round vesicular nuclei which occupied almost the entire cell. Some cells tended to be spindle-shaped. Mitoses were prominent though for the most part regular in form. Diagnosis was made of sarcoma of mesoblastic origin. This patient died a few weeks later and at autopsy diagnosis of spindle-celled sarcoma of the retroperitoneal space was substantiated. In addition, numerous metastatic nodules were found in the liver and lungs which showed an adenomatous structure consistent with metastases of the original adenocarcinoma of the fundus.

13. LYMPHOBLASTOMA

CASE 14.—H. H. (No. 317246.) (Courtesy Dr. C. T. Bingham.) Patient aged forty-nine years, para iii. Biopsy showed a typical lymphoblastoma. This patient died about two months after exploratory operation and at autopsy diagnosis was confirmed. Death occurred from uremia caused by blockage of both ureters by the tumor. Deep x-ray therapy was only of temporary value. It was notable in this patient that there was no general glandular or splenic enlargement.

14. CHORDOMA

The recent review of chordomas by R. E. Babrey[8] calls attention to this fatal type of tumor originating from fetal notochord. Those of interest to the gynecologist are particularly the antesacral variety, of which 41 were reported out of 150 in the literature. These tumors have a tendency to surround the rectum, the infiltration and fixation being even more extensive than in carcinoma of the rectum.

CASE 15.—H. H. (No. 314266.) (Courtesy Dr. W. Standish.) Patient, aged three years, presented a mass in the left inguinal region, and one the size of a golf ball just in front of the coccyx and behind the rectum, of about three to six weeks' duration. Biopsy obtained under anesthesia, at which time careful rectal examination was done which showed a friable gray cellular tissue having no definite capsule, and in some areas being slightly opalescent. This was made up of neoplastic cells, lining and almost filling irregular spaces, sometimes in papillary formation. The cells were irregular in shape with a very sharp cell margin and a clear vacuolated cytoplasm containing large, oval or round nuclei with rather delicate chromatin network. The nucleoli were poorly seen, small, and frequently multiple. There were many mitoses and considerable anaplasia. Diagnosis was made of a malignant tumor, probably an embryonal carcinoma, possibly a chordoma. This patient died shortly after leaving the hospital with metastases in the spine and lungs. Deep x-ray radiation had little effect.

15. RETROPERITONEAL DERMOIDS OR TERATOMAS

No instances were noted of retroperitoneal dermoids or teratomas. Ewing[4] classifies three types: (1) tridermal teratomas, (2) epidermoid rests of wolffian duct, and (3) true dermoids. He states that dermoid cysts of the pelvic connective tissue are rare.

At the onset of this study, it was hoped to present a classification of retroperitoneal masses which the gynecologist might expect to encounter. It soon became evident, however, that a complete catalogue of all the tumors which have been recorded as arising in this region would resemble a treatise on general pathology. As far as neoplasms are concerned, classification of neoplastic diseases offered by Ewing for the whole body would serve equally as well for the retroperitoneal region. Suffice it to say that the operator must bear in mind the various possibilities, rare though they may be.

SUMMARY

Attention has been called to the great variety of neoplasms and other masses which may be encountered in the retroperitoneal tissues in and about the pelvis. Brief case histories of instances coming under observation have been given.

For the gynecologist to treat successfully the wide variety of lesions which may be encountered, it is necessary for him to know well the anatomy of this region, especially its blood and nerve supply, and also to understand various pathologic processes which may surprise him.

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DISCUSSION

DR. I. C. RUBIN, New York, N. Y.—Among 5,600 cases admitted to the Gynecological Service of the Mount Sinai Hospital for a period of eight years there were 4 that could come under this grouping of retroperitoneal pelvic tumors. Two were referred to by Miller, and reported by Frank, a lymphangioma and a schwannoma. The incidence was about one in 1,400 cases.

Iliac lymphadenitis is not, properly speaking, a retroperitoneal tumor. This type of pelvic mass occurs perhaps a little more frequently than is commonly appreciated. Nor are sacral kidneys retroperitoneal tumors, in the strict pathologic sense.

There is apparently a reason for the infrequency of pelvically placed retroperitoneal tumors. Retroperitoneal tumors, especially the solid variety, arise as a rule from the three organs, namely, the pancreas, the kidneys, and the suprarenals. In the female pelvis such tumors may also originate from the Wolffian and Gärtner's ducts, or from components of the ovary.

One of the retroperitoneal cysts that we encountered was a tumor occupying the entire abdomen and presenting a picture of a woman at term pregnancy. It was possible to feel the lower pole of the tumor by bimanual examination. There was a fluid wave in both flanks. An intravenous urograph failed to give us any aid because of lack of concentration of the dye. By transuterine pneumoperitoneum, a huge mass was demonstrated in the abdomen which was neither connected with the liver nor the spleen, nor with the depth of the pelvis. Its fixation moreover gave us the impression that we were dealing with a retroperitoneal cyst. At laparotomy the tumor was found to arise from behind the posterior parietal peritoneum, to the right of the ascending colon. It was shelled out readily as far as the junction of the ureter to the pelvis of the right kidney which was found to be hydronephrotic. We thought it might therefore be a cyst of the kidney, but when removed it was shown to be a simple cyst with an endothelial lining, some smooth muscle strands and connective tissue, in other words, a large retroperitoneal cyst which had nothing to do with the kidney itself.

There is one kind of cyst that has not been emphasized by Dr. Miller and which is more commonly encountered by gynecologists. In this type the lower pole reaches almost to the level of the perineum, and we all know how difficult it is to shell it out from its deepest portion. Occasionally it is necessary to marsupialize it in order not to make the operation too extensive.

The tumors that I have just referred to as being supposedly of inflammatory nature, the tumors that give rise to pelvic tenesmus, and which lead you down into the obturator fascia, are properly classified, I think, as retroperitoneal tumors be-

cause they most likely arise from the rests of the Wolffian and Gärtner's ducts, which are commonly met with in that area. They are ordinarily regarded as intraligamentous cysts but may properly be called retroperitoneal cysts.

DR. ALEXANDER M. CAMPBELL, GRAND RAPIDS, MICH.—I wish to report an unusual case of a woman who was referred to us recently with the diagnosis, by her family physician, of ovarian cyst. The abdomen was almost the size that one would find in a full-term pregnancy. The only disturbance from which she suffered was shortness of breath.

A pelvic examination revealed a normal uterus and normal ovaries. On an exploratory operation we discovered an enormous retroperitoneal cyst which was approached by opening the gastrocolic omentum and stitching the posterior peritoneum to the parietal peritoneum and leaving a large circular opening exposed for a week. This opening was packed with gauze and on the eighth day the cyst was evacuated and five quarts of a chocolate fluid were taken from this cyst. The fluid had digestive qualities. A portion of the capsule of the tumor was removed for pathologic examination and the cyst showed no epithelial lining. It was undoubtedly an inflammatory cyst of the pancreas. The cyst cavity was packed with iodoform gauze and it is gradually closing.

RADIUM IRRADIATION FOR BENIGN HEMORRHAGE

WITH A TWO TO TWENTY-YEAR REVIEW OF 1437 CASES

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RADIUM irradiation is now generally accepted as the method of choice in the treatment of certain types of uterine hemorrhage of benign origin. The chief disadvantage of the treatment is that its success is dependent largely, if not entirely, upon the inhibiting or destructive action of the irradiation upon the ovarian endocrine system. This destructive action is one that should definitely be considered in evaluating this method of treatment. Many surgeons are prone to base the success or failure of the treatment solely by the effect it has on the hemorrhage.

The following report is the result of a study made of all patients with benign uterine hemorrhage treated with intrauterine radium irradiation in the Gynecologic Division of the Hospital of the University of Pennsylvania from 1916 to 1935 inclusive. In addition to the reports of the routine follow-up, and with a view to bringing the records up to date and determining, as far as possible, the ultimate outcome of each case, a questionnaire was sent to each patient. Those cases residing in or near Philadelphia were requested to return for examination and personal interviews. In all, 1,437 patients treated by radium irradiation for benign hemorrhage were studied; including 750 cases of functional

hemorrhage and 687 cases of myomas. Of these, 1,006 patients have been followed for two years or more (521 functional hemorrhage and 485 myoma uteri). Records of 184 of the myoma cases and of 116 cases of functional hemorrhage are available for follow-up study, for periods covering from ten to twenty years. Many patients were examined and questioned personally. As regards the development of menopausal symptoms induced by the irradiation, the patient's own statement has been the criterion upon which the statistical study is established. The fact that our personal opinion, based upon answers received at interview with patients, does not always accord with the patient's view, has not been considered in deciding this point. Thus some patients stated that the menopausal symptoms were severe, whereas questioning brought out the fact that they were probably mild and caused but little discomfort; in other instances, it appeared that the menopause developed in a normal manner. It is obvious, therefore, that it is difficult to determine this accurately since the pain and discomfort thresholds vary so markedly in different patients. In passing, it may be stated that the group interviewed personally yielded decidedly better results in this respect than did the answers secured from the questionnaires.

Although the severity and duration of the menopausal symptoms that may develop after irradiation are of importance in evaluating the results of the treatment, this is, as previously stated, a difficult point to determine with accuracy, particularly when dealing with answers to questionnaires. For this reason, this feature is not stressed in the following report; it has been dealt with in detail in the study by Keene and Payne* published in 1933. No result has, however, been classed as satisfactory in which the patient stated that the menopause was so severe that it incapacitated her or in which the pathologic bleeding was not relieved permanently.

The results secured in the myoma and in the functional hemorrhage cases have been separated. A special effort has been made to analyze such late results and complications as might develop ten or more years after irradiation, as well as the effect of the treatment upon fertility and subsequent pregnancy.

As a routine measure a preliminary diagnostic curettage was performed in each case. No case of carcinoma has ever been overlooked, with possibly one exception. This was a case in which a histologic diagnosis of hyperplasia was made; seven and one-half months later a second curettage was performed and carcinoma was diagnosed. Hysterectomy was performed and a carcinoma measuring 1 by 0.5 by 0.5 cm. was found in one cornu.

Indications.—In the John Goodrich Clark Clinic the indications for radium irradiation in the class of cases under discussion have changed but little since 1916, although dosage and filtrations have undergone

*Keene, Floyd E., and Payne, Franklin L.: Surg. Gynec. Obst. 56: 322, 1933.

modifications. Our indications for radium therapy for benign hemorrhage are: patients suffering from pathologic bleeding in whom more conservative measures have failed, who are at or near the menopause and in whom other pelvic complications are absent; in the myoma group, patients having tumors not larger than a four months' pregnancy. Numerous patients not entirely ideal have also been treated by irradiation, the associated conditions being such as to make hysterectomy unduly hazardous or undesirable.

Contraindications.—The contraindications to irradiation are:

1. When doubt exists as to the accuracy of the diagnosis.
2. The presence of intraperitoneal lesions other than those responsible for the bleeding and which require surgical intervention.
3. Rapid growth in the case of a supposed uterine myoma.
4. Associated fundal carcinoma.
5. Pressure symptoms.
6. Softening or other evidence of degeneration.
7. Inflammatory lesions within the pelvis, especially those of the adnexa.
8. The presence of neoplasms larger than a four months' pregnancy.
9. Submucous tumors, especially, if they are pedunculated.
10. Myomas in young women.
11. Anemia markedly out of proportion to the bleeding.
12. Obstructing tumors or malformations that prevent the proper application of the radium.
13. Radiophobia.
14. The presence of cervical myomas.
15. Pregnancy.
16. Highly nervous women.
17. Previous pelvic operations.
18. Painful myomas.
19. Myomas after the menopause.

These indications and contraindications are not governed by a hard-and-fast rule; for example, an associated cardiac lesion may make irradiation of a myoma advisable which otherwise would be treated by hysterectomyomectomy; or in an associated fundal carcinoma irradiation may be the method of choice because of extreme obesity or for other special reasons.

In the analysis of the group of cases discussed in this paper it should be remembered that there are included a large number of the patients suffering from severe anemia, due either to functional hemorrhages or to myomas, who have entered our clinic during the last twenty years. Although we are aware that this type of case is not ideal for irradiation, we have often been forced to resort to this method of treatment when more conservative measures failed. In recent years, most of our patients who were markedly anemic have received preliminary blood transfusions. Furthermore, the John Goodrich Clark Clinic was one of the pioneers in the use of radium in America, and therefore dosage and technic were not so well established in the earlier cases as they are at

the present time. Many of these patients were treated before the subject of endocrinology had been developed and could neither be studied nor treated for hormonal imbalance. Nevertheless, the series under discussion embraces all patients treated during this more or less experimental period.

A large proportion of our patients with functional bleeding had been treated by medical measures without result. In the more recent groups medical measures had been supplemented by endocrine therapy in a number of cases. Curettage had been previously performed elsewhere in a proportion of cases and in these irradiation was resorted to only after failure of the more conservative measures.

From 1916 to 1931, the radium filtration was 1 mm. of brass or 0.5 mm. of platinum; from 1931 to 1935, 1 mm. of platinum was employed. An additional filter of 2 mm. of red rubber tubing has been used routinely.

Optimum Dosage.—If a dosage large enough to destroy the ovarian function is administered, complete cessation of bleeding can be secured in practically all cases. As a result of such treatment, however, the irradiation menopause is established. The severity and character of the symptoms are the same as those of the menopause which follows a bilateral oophorectomy. Loss of ovarian function causes varying degrees of discomfort and is dependent upon many factors, the nervous stability of the patient, her age, temperament, and many other conditions.

The menopause was one of the chief subjects discussed before the Eighth Congress of the Association of Gynecologists and Obstetricians of the French Language. At this meeting, Barrett and other members of a committee reported that, among 1,000 women studied, 89.7 per cent were able to carry on their usual occupations without interruption during the menopause, and that 15.8 per cent were entirely free from unpleasant symptoms during this period.

The great majority of patients suffering from benign hemorrhage are under forty-five years of age, and a considerable proportion are much younger. In other words, a relatively large number of these patients may be expected to undergo discomfort as a result of a castrating dose of radium, and a definite percentage will suffer acutely for years. Furthermore, some of these patients are in the childbearing age, and the sterilization that results from irradiation is a factor to be taken into serious consideration. This applies especially to those patients suffering from functional hemorrhage, who, considered as a group, are younger than those who suffer from myomas.

In contrast to the disadvantages just described must be mentioned the efficacy of the treatment in arresting hemorrhage, its low attendant mortality and morbidity, and the shortness of the period of convalescence. The fact that surgery is by no means always the ideal method of treatment should also be taken into consideration. The point which

we wish to stress is that radium is a highly potent and, so far as ovarian function is concerned, a destructive agent. In spite of this unfavorable action, irradiation is the most satisfactory method of treatment at our command at present in certain cases.

An important point to be borne in mind is that the selection of cases for irradiation and the dosage should be carefully considered. Irrevocable damage may be done by ill-advised irradiation. The efficacy of the remedy in stopping hemorrhage and the ease with which it may be applied constitute definite hazards in this form of treatment, particularly in patients in the childbearing period. As a result of these observations, efforts have been made to modify the dosage of radium so that hemorrhage will be checked but without completely sacrificing the ovarian function. Of course, it is obvious that a dosage of this size is less certain and less permanent in its results, but is, we believe, the method of choice. To determine the ideal dosage is by no means easy, and it is only by a careful and unbiased analysis of the end-results in groups of cases during the various decades that even an approximately safe and effective dosage can be arrived at. It is our belief that in the past, particularly in the earlier cases, too heavy irradiation has been employed. This applies especially to the younger group of patients.

Table I shows the percentage of menopausal symptoms that developed in 496 of the patients irradiated for *functional hemorrhage*, arranged according to age.

TABLE I. PERCENTAGE OF PATIENTS EXHIBITING MENOPAUSAL SYMPTOMS AFTER IRRADIATION FOR FUNCTIONAL HEMORRHAGE (496 CASES)*

AGE IN YEARS	PATIENTS IRRADIATED NUMBER	MENOPAUSAL SYMPTOMS PER CENT
Less than 20	15	33
20 to 30	74	24
30 to 40	137	67
40 to 50	229	68
Over 50	41	70

*Note low incidence of menopausal symptoms in patients less than thirty years of age. Definite information regarding menopausal symptoms was not available in 25 additional cases followed up.

Table II shows the percentage of menopausal symptoms that developed in relation to age in 471 of the patients irradiated for *uterine myomas.*

TABLE II. PERCENTAGE OF PATIENTS EXHIBITING MENOPAUSAL SYMPTOMS AFTER IRRADIATION FOR MYOMAS (471 CASES)*

AGE IN YEARS	PATIENTS IRRADIATED NUMBER	MENOPAUSAL SYMPTOMS PER CENT
Less than 30	9	33
30 to 40	76	81
40 to 50	288	57
Over 50	98	55

*Definite information regarding menopausal symptoms was not available in 14 additional cases followed up.

Tables I, II, and III, indicate that among the patients under thirty years of age, menopausal symptoms following irradiation were present in about 30 per cent of cases. The relative infrequency of the menopausal symptoms in these groups as compared with those made up of

TABLE III. PERCENTAGE OF PATIENTS EXHIBITING MENOPAUSAL SYMPTOMS AFTER IRRADIATION FOR FUNCTIONAL HEMORRHAGE AND MYOMA UTERI

AGE IN YEARS	PATIENTS IRRADIATED NUMBER	MENOPAUSAL SYMPTOMS PER CENT
Less than 20	15	33
20 to 30	83	29
30 to 40	213	71
40 to 50	517	62
Over 50	139	56
Total	967	59

older patients may perhaps be explained by the fact that the average dosage was considerably smaller among the former and that the ovaries of young women are probably more resistant to the destructive action of the rays than are those of the older patients, or they may recover more easily from the effects of treatment.

Table IV shows the total number of patients who have become pregnant following irradiation, the total number of pregnancies, and the condition of the fetuses at the termination of pregnancy. The infrequency with which pregnancy occurred, and the high percentage of nonviable fetuses in this series are worthy of note.

TABLE IV. POSTIRRADIATION PREGNANCIES IN ENTIRE SERIES

DIAGNOSIS	PATIENTS IRRADIATED	PATIENTS PREGNANT	TOTAL PREGNANCIES	LIVING CHILDREN	NONVIABLE FETUSES	UNDELIVERED PREGNANCIES
Functional hemorrhage	521	18*	28	12	13	3
Myoma uteri	485	2	3	3	0	0
Total	1006	20	31	15	13	3

*Two patients with questionable early pregnancies at last follow-up not included.

Table V is a detailed summary of the patients who have become pregnant following irradiation, as well as the number of stillbirths, miscarriages, and abortions.

In our series of cases, pregnancy following irradiation has been of infrequent occurrence, probably because relatively few of the patients who were subjected to this form of treatment were in the childbearing age. Furthermore, myomas were present in nearly half of the patients, and since these neoplasms tend in themselves to produce sterility, this is also a factor in preventing conception, as well as in producing abortion if conception should take place. In the cases of functional hemorrhage, endocrine imbalance may explain the high proportions of sterile patients and the frequency of nonviable fetuses.

As a result of his extensive clinical and experimental studies, Douglas P. Murphy reached the conclusion that preconception irradiation had little if any effect upon subsequent pregnancies, except to cause sterility. The number of patients in our series in whom pregnancy followed irradiation is a small one, far too small to permit conclusions to be drawn regarding the fate of the embryo.

TABLE V

A. Summary of Pregnancies Following Irradiation for Functional Hemorrhage

4 patients	Each, 1 full-term pregnancy
1 patient	2 full-term pregnancies
1 patient	1 full-term pregnancy; 1 premature delivery, the infant living two days
1 patient	1 full-term pregnancy (toxemia); 1 full-term pregnancy; 1 miscarriage
1 patient	1 full-term pregnancy; 2 stillbirths
1 patient	1 stillbirth
1 patient	2 stillbirths
1 patient	7 months' premature infant
1 patient	1 miscarriage; again pregnant at time of last follow-up
1 patient	3 miscarriages
2 patients	Each, 1 miscarriage
1 patient	1 induced abortion for therapeutic reasons
2 patients	Each pregnant last follow-up
1 patient	1 possible miscarriage
1 patient	1 questionable pregnancy last follow-up

B. Summary of Pregnancies Following Irradiation for Myomas

1 patient	1 premature pregnancy, the infant living
1 patient	2 full-term pregnancies

Table VI shows the proportion of menopausal symptoms following irradiation and the satisfactory results secured in the functional hemorrhage cases.

TABLE VI. PROPORTION OF MENOPAUSAL SYMPTOMS AND SATISFACTORY RESULTS FOLLOWING IRRADIATION IN VARIOUS DOSAGES FOR FUNCTIONAL HEMORRHAGE

RADIUM DOSAGE MG. HR.	NUMBER OF PATIENTS	MENOPAUSAL SYMPTOMS PER CENT	NUMBER OF PATIENTS	SATISFACTORY RESULTS PER CENT
500 or less	219	42	231	75
600-1000	118	70	120	83
1200-1500	135	80	141	92
1500 and over	24	79	29	83
Total	496*	61	521	82

*Definite information regarding menopausal symptoms could not be obtained in every case followed up, but was available in the vast majority.

TABLE VII. PROPORTION OF MENOPAUSAL SYMPTOMS AND SATISFACTORY RESULTS FOLLOWING IRRADIATION IN VARIOUS DOSAGES FOR MYOMA UTERI

RADIUM DOSAGE MG. HR.	NUMBER OF PATIENTS	MENOPAUSAL SYMPTOMS PER CENT	NUMBER OF PATIENTS	SATISFACTORY RESULTS PER CENT
500 or less	35	58	42	67
600-1000	123	55	125	86
1200-1500	271	59	275	84
1500 and over	42	57	43	81
Total	471*	56	485	85

*Definite information regarding menopausal symptoms could not be obtained in every case followed up.

In connection with Table VIII, it will be noted that the menopausal symptoms are materially less in patients who received a dosage of less than 600 mg. hours, but the satisfactory results secured are correspondingly diminished with the smaller dosage. The effect of irradiation in dosages over 600 mg. hours was practically constant both in regard to the percentage of menopausal symptoms produced and the satisfactory results achieved.

TABLE VIII. PROPORTION OF MENOPAUSAL SYMPTOMS AND SATISFACTORY RESULTS FOLLOWING IRRADIATION IN VARIOUS DOSAGES FOR ENTIRE FOLLOWED-UP SERIES

RADIUM DOSAGE MG. HR.	NUMBER OF PATIENTS	MENOPAUSAL SYMPTOMS PER CENT	NUMBER OF PATIENTS	SATISFACTORY RESULTS PER CENT
500 or less	254	44	273	74
600-1000	241	62	245	85
1200-1500	406	65	416	89
1500 and over	66	62	72	83
Total	967*	59	1006	83

*Definite information regarding menopausal symptoms could not be obtained in every case followed up.

Table IX shows the infrequency with which unfavorable complications or recurrences were encountered in the 300 patients in this series ten years or more after they had been irradiated.

TABLE IX. RECURRENCES OR COMPLICATIONS OCCURRING TEN YEARS OR MORE AFTER IRRADIATION

DIAGNOSIS	NUMBER OF PATIENTS FOLLOWED UP 10 YEARS OR MORE	RECURRENCES OF COMPLICATIONS	
		NUMBER	PER CENT
Functional hemorrhage	116	5	4
Myoma uteri	184	4	2
Combined total	300	9	3

Table X summarizes briefly the results secured in those cases of functional hemorrhage in which one irradiation failed to produce satisfactory results, together with the final outcome.

TABLE X. UNSATISFACTORY RESULTS FOLLOWING ONE IRRADIATION FOR FUNCTIONAL HEMORRHAGE; SUBSEQUENT TREATMENT; FINAL RESULT

INITIAL TREATMENT UNSATISFACTORY RESULT NUMBER OF PATIENTS	SUBSEQUENT TREATMENT	FINAL RESULT SATISFACTORY NUMBER OF PATIENTS
49	Reirradiation	49
17	Hysterectomy	14
5	Pelvic surgery	5
12	Hormone therapy	12
3	Not stated	3
6	No treatment	0
Total 92		83

Table XI shows the final outcome among the cases of uterine myoma in which one irradiation failed to secure satisfactory results.

TABLE XI. UNSATISFACTORY RESULTS FOLLOWING ONE IRRADIATION FOR MYOMA UTERI; SUBSEQUENT TREATMENT; FINAL RESULT

INITIAL TREATMENT UNSATISFACTORY RESULT NUMBER OF PATIENTS	SUBSEQUENT TREATMENT	FINAL RESULT SATISFACTORY NUMBER OF PATIENTS
37	Reirradiation	37
31	Hysterectomy	30
3	Myomectomy	2
1	Oophorectomy	0
1	Exploratory	0
1	No treatment	0
Total 74		69

TABLE XII. PELVIC CARCINOMA DEVELOPING IN PATIENTS AFTER IRRADIATION FOR FUNCTIONAL HEMORRHAGE AND MYOMA UTERI

DIAGNOSIS	PATIENTS IRRADIATED NUMBER	PELVIC CARCINOMA NUMBER
Functional hemorrhage	521	4
Myoma uteri	485	7
Total	1006	11
Extrapelvic carcinoma developed in 5 additional patients		

TABLE XIII. OPERATIVE MORTALITY—ENTIRE SERIES

DIAGNOSIS	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY PER CENT
Functional hemorrhage	750	1*	0.13
Myoma uteri	687	3†	0.4
Total	1437	4	0.278

Causes of Death: *_Vincent's Angina_ seven days after irradiation.

†1. _Pneumococcic Meningitis_ on the third day. This patient had an ulcer of the nasal septum on admission. 2, _Cerebral hemorrhage_ on the fifth day. 3. _Intestinal Obstruction_ on the tenth day.

CONCLUSIONS

1. To secure good results from irradiation, the cases must be carefully selected; this requires not only correct judgment, but diagnostic and histologic skill.

2. The destructive effects of irradiation, while being the direct means by which the hemorrhage is checked, also constitute a definite drawback to this form of treatment.

3. In a study of 1,437 cases of benign hemorrhage treated by means of intrauterine radium irradiation, 750 were cases of functional hemorrhage, and 687 of myomas. One thousand and six patients of the

entire series were followed up for two years or more, and 300 of these patients have been observed over a period varying from ten to twenty years.

4. Menopausal symptoms occurred in 59 per cent of 967 reported cases of functional hemorrhage and myomas.

5. Satisfactory results were secured in 83 per cent of the group of cases.

6. The myoma cases yielded about the same proportion of satisfactory results as did the functional hemorrhage cases.

7. Three per cent developed relapses or complications requiring treatment ten or more years after irradiation.

8. The proportion of cases in the followed-up group in which carcinoma of the genital tract developed after irradiation was 1.09 per cent.

9. The mortality in the entire group was 4 patients or 0.278 per cent.

133 South Thirty-Sixth Street

DISCUSSION

DR. JAMES E. KING, Buffalo, N. Y.—In this series presented I am sure that many will feel that ovarian function has been destroyed too often. I believe it is a mistake to induce the menopausal symptoms in women under forty. I have always found it far simpler to explain to a young woman why her abnormal bleeding returns than to console her after the induction of a premature menopause.

My own practice has been to use small doses of radium in women under forty, and the larger doses in women past forty-five. In the former one can only regard the treatment as palliative and in about 30 per cent of these cases subsequent treatment will be required.

From 1922 to 1936, a fourteen-year period, I personally irradiated 226 fibroids. Approximately 70 per cent of these were associated with hyperplasia. In the remaining 30 per cent, the scrapings were reported as premenstrual swelling or in the absence of tissue they were regarded as an atrophic endometrium. There is little definite knowledge as yet to justify a diagnosis of "endocrine bleeding."

During the past three years in three of my patients irradiated for benign bleeding a subsequent pregnancy required cesarean section for dystocia due to the failure of the lower uterine segment to dilate. In one case the uterus was removed and the pathologist reported the condition as being due to cicatricial tissue. Following these cases the radium was packed high into the fundus.

I have a few slides showing the results of irradiating 114 fibroids in the five-year period from 1927 to 1931. It was possible to follow 104 of these cases. Of these 104 cases, 85, or 81 per cent, were "cured" either by a correction of the abnormal bleeding or in the older patients by the production of the menopause. Four of these 104 patients have had labors at term. Fourteen of the 104 were subsequently advised to have an operation. Ten hysterectomies were done, one large submucous polyp was removed and three refused surgery.

Hyperplasia was found in 71 per cent of the 114 cases. This large percentage strongly suggests a definite relationship between fibroids and endometrial hyperplasia, and very possibly the same etiologic factor is concerned in the production of both.

DR. FRANK A. PEMBERTON, BOSTON, MASS.—We have treated only 90 fibroids with radium because my former chief, Dr. Graves, thought that operation was better on the whole than radium. I am going to confine my discussion to cases of functional bleeding.

We have treated 762 patients and have been able to follow 425, or 83 per cent, two or more years. We have divided them into two groups. In one we did not want to cause change of life, while in the other group we did wish to. In the first group are 131 patients, 14 per cent of whom are under twenty years of age, 31 per cent between twenty and twenty-nine, 50 per cent between thirty and thirty-nine. In the group where we wanted to cause change of life there were no patients under twenty, only one up to thirty, 18 per cent between thirty and thirty-nine, and the great majority over forty.

Among the 131 patients in whom we did not want to cause change of life, 86 were regarded as cured, 8 were relieved to the extent that their profuse flowing stopped, but they had irregular periods, and 8 required another radium treatment. In this group of cases we used from 200 to 500 mg. hours, rarely more than 400 mg. hours. Four, all thirty years old or over, we count as failures because we caused amenorrhea. Seventy-eight per cent of this group gave satisfactory results, which is about the same as Behney's. In 13 patients we had to use secondary treatment as follows: hysterectomy, 6; radium to cause the menopause, 6; and x-ray treatment, 1. The other 12 out of the total went elsewhere for further treatment.

The second group consisted of 294 patients. One (0.3 per cent) was under thirty years of age and only 56 (18.7 per cent) were under forty. The results were satisfactory in 283 (96 per cent). The dosage varied from 800 to 1,600 mg. hours with a few of 2,400. Secondary treatment was required in the other 11 and consisted of hysterectomy in 8 and more radiation in 3.

In the first group of 131 cases there were 35 pregnancies among 24 patients. These occurred in patients who had normal periods following only one radium treatment. They had 20 normal babies, 7 stillbirths, and 9 miscarriages, which I think again agrees approximately with Behney's figures.

We follow the same indications for treatment that Behney uses. As regards the symptoms of menopause, we feel that they are about the same as those following operation. They are more likely to be severe in nervous and highly strung women, and therefore we operate on such patients and conserve an ovary. These represent, however, a small percentage of all cases.

There were 4 patients out of 425 who developed intrapelvic tumors after treatment. One was a twenty-six-year-old woman who was admitted to another hospital six years later for an inoperable pelvic tumor, the character of which was not determined. The second was a thirty-six-year-old woman. She was discovered by a survey of the death records at the State House to have died, six years after our treatment, of cancer of the cervix. It is very possible that she had cervical cancer at the time we treated her, but it was so small that we missed it. The third patient was found to have a cancer of the endometrium eleven years after our treatment, and the fourth, a forty-six-year-old woman, died of general abdominal carcinomatosis, probably originating in the ovary, fifteen years after our treatment. We do not feel responsible for any of these except possibly the second one.

DR. WALTER T. DANNREUTHER, NEW YORK, N. Y.—I can refer only to a modest series of 183 patients treated personally during a thirteen-year period. In the main, the results in this small group do not differ materially from those reported by Behney. He has truly stated that the cases must be carefully selected, and has outlined the contraindications for radium therapy, which conform with the prevailing opinion of most gynecologists.

It would also be of interest to know the number of patients in whom menstruation was reestablished after the irradiation. The preservation of the menstrual function, together with 31 pregnancies eventuating in 15 living children, would seem to cast some doubt on the statement that "the success of the treatment is dependent largely, if not entirely, on the inhibiting or destructive action of the irradiation on the ovarian endocrine system." The contraction of fibromyomas and the fibrosis of the myometrium following irradiation, with the continuation of menstruation in so many cases, can justly be regarded as additional evidence that there is at least some local effect on the uterus which contributes to the arrest of the normal bleeding.

The inclusion of 15 patients less than twenty-one years of age is somewhat surprising, as the treatment of the bleeding of puberty or adolescence can nearly always be satisfactorily controlled by other methods.

My experience has been that about 18 per cent of white patients with fibroids requiring treatment are suitable candidates for radium therapy; that the menstrual function will be preserved in 78 per cent of cases when the dose is 750 mg. hours or less; and that in 13 per cent of cases it has a depressing effect on sexual inclinations. There have been 6 pregnancies in 4 of my 183 patients, resulting in 4 living children. There has been no mortality.

DR. EARDLEY HOLLAND, LONDON, ENGLAND.—Many of the climacteric cases have leucorrhea after radiation, but we have been able to diminish the incidence of this a great deal by careful secondary screenage of the platinum retainer which we think has an atrophic effect on the endometrium.

An important question is whether radium in the uterus has any effect in increasing the incidence of cancer of the body of the uterus. There are some authors who believe that. I do not believe that there is any connection, but it must be definitely settled one way or the other.

It is also important to make a most careful investigation in every case of functional hemorrhage. Every patient should have a complete blood examination, including coagulation time, bleeding time, and metabolic rate. Otherwise we shall find ourselves producing a menopause in patients who have nothing more than hypothyroidism. Years ago I introduced radium into the uterus of a girl of twenty-one because she had formerly had an attack of bleeding which finally had been stopped. She was ultimately cured of purpura by splenectomy.

Some patients are very vague in reporting menstrual histories, and we found it very difficult to get a good record of uterine hemorrhage. I have therefore devised some graphic uterine hemorrhage charts which I have used for my students who find them of enormous help. This is a chart I use in all cases where there is a history of regular menstruation. It is divided into months and shows the days up to 31. If the patient has what we call spotting of blood, it is shown by a little spot; average menstruation is shown by one square; a show of blood is indicated by a little streak; excessive bleeding is shown by two squares; flooding, by three squares. Of course, these do not pretend to be accurate measurements but it simply gives a graphic history.

For example, here is shown a patient's history recorded in this way. She was a woman of fifty-two with climacteric hemorrhage, who came to me having had normal periods in November and in December, and then another so-called period three days after that. She menstruated perfectly normally for the next few months and then her doctor brought her in again because she had had a normal period, a prolonged period, and then severe bleeding. Since her hemoglobin was only 26 per cent, she was given a blood transfusion, a radium treatment, and Blaud's pills. Her hemoglobin went up to 80 per cent and she is now perfectly well.

May I suggest that if you take your histories in this way you will have a graphic account of the patient and your students will appreciate it immensely. Those of you who are in the habit of giving hormone treatment will find it very useful for such recording.

DR. NORRIS (closing).—An endeavor has been made in this paper to point out that irradiation is not an ideal treatment, although it is believed the best for certain types of cases. Certainly the functional cases should, at least theoretically, be treated along the lines of endocrine therapy. It is now routine with us to attempt conservative treatment, which includes endocrine therapy, in all women suffering from functional uterine hemorrhage who are in the childbearing age. Irradiation is advised only after these methods have failed.

I had thought before our follow-up was completed that we would find results in the myoma cases not as satisfactory as in a corresponding group of the functional cases, but as a matter of fact all through this series it was about the same. I think we irradiate perhaps one case in five where a symptom-producing myoma is present.

The condition of the postradiated endometrium is a subject which has interested me very much. I have personally examined perhaps 50 uteri, in which there have been irradiation six months or more previously, and have yet to see a case where there was any gross pathologic evidence of the treatment. I have sectioned most of these uteri and in only one or two have I been able to see anything under the microscope that indicated previous irradiation, other than senile changes which were general throughout the endometrium. Theoretically I think there must be some scar tissue due to irradiation, but it plays no part in the final result.

There are two prices which the woman who is subjected to irradiation instead of operation pays. One of them is that a certain proportion will suffer from discharge for about six weeks, sometimes for three months, and sometimes a little longer. That is one minor drawback. The other is that the patient will have to return regularly for a follow-up for a prolonged period of time. This is particularly true in the myoma group, where the tumor is still present after treatment, and we do not know exactly what may happen to it.

It is hard to determine the proportion of carcinoma which developed in this series, and whether or not it is out of proportion to the normal carcinoma incidence. We all feel, I think, that chronic irritation plays a part in the predisposition to carcinoma. After irradiation there is chronic irritation but for a relatively short time only. Another factor is that irradiation patients have a longer cancer age, since it is probably the sex age of the individual which is a predisposing factor to cancer rather than the actual age in years.

Perez and Arenas: Myiasis of the Vulva, Bol. Soc. de obst. y Ginec. (Buenos Aires) **14**: 849, 1935.

The authors report 2 cases of myiasis of the vulva. The rarity of finding the larvae of the fly in this location they feel is due to the natural protection of these parts. It is not rare to find myiasis of the auditory canal, nares, etc.

In both cases there was localized swelling of the labia, and a canalization of the skin, from openings of which from 8 to 10 larvae were extracted. The treatment consisted in washing out the cavities with chloroform water and applications of thymol into the cavities. Both patients were cured in about ten days. The authors find only 4 other cases reported in the literature.

MARIO A. CASTALLO.

RELATION OF ENDOMETRIAL HYPERPLASIA TO ADENOCARCINOMA OF THE UTERUS

EMIL NOVAK, M.D., BALTIMORE, MD., AND ENMEI YUI, M.D., SHANGHAI, CHINA*

(From the Gynecological Department of Johns Hopkins Medical School)

IN THE overwhelming majority of cases, hyperplasia of the endometrium is, from a pathologic standpoint, a frankly benign lesion. In a small minority of cases, however, it presents proliferative features which tax the judgment of the pathologist who is called upon to decide whether or not they are indicative of malignancy. With most of these borderline pictures, one who is familiar with the proliferative vagaries of hyperplasia will usually, though not always, decide against actual cancer; but the further question arises as to whether a lesion which can present such cancer-like features may not at times step over the line and give rise to genuine cancer—whether, in other words, it is not to be looked upon as a precancerous lesion, in the usual sense of that much-abused but not unuseful term, i.e., as indicating a lesion which predisposes to cancer rather than one which represents a transition from benign to cancerous disease.

It is with this general problem in mind that we have recently restudied all the cases of endometrial hyperplasia and of adenocarcinoma of the uterine body which have passed through our laboratory during the past eleven years. During this period, a total of 12,813 case specimens has been reviewed. Among these we have encountered 804 cases of endometrial hyperplasia and 104 of corporeal adenocarcinoma. With the hyperplasia cases we have been chiefly concerned in sifting out those in which there has been evidence of unusual proliferative activity, producing pictures which histologically would seem to constitute varying degrees of approach to that of cancer itself. In the adenocarcinoma group the natural plan of such a study as ours, and the one which we have followed, is to determine how frequently cancer has occurred in uteri showing also hyperplasia, and how frequently the antecedence of hyperplasia is indicated by previous histological studies or by the clinical history.

Until recent years most authors have been inclined to deny to hyperplasia any such predisposing influence in the development of cancer; as, for example, many have ascribed to such lesions as leucoplakia of the cervix, cervical irritation or erosion, Schimmelbusch's disease of the breast, or gastric ulcer, and certainly far less than to leucoplakia of

*Dr. Yui's part in this work was made possible by the Mary Putnam Jacobi Fellowship of the Women's Medical Association of New York City.

the vulva. This was formerly the view held in our own laboratory, as expressed in the paper of Novak and Martzloff in 1924, and in several other publications both before and after this. Similar opinions have been expressed by numerous other writers (Schröder, Shaw, Cullen, Burch). In the most recent paper on the subject, L. E. Burch states that "I have never seen the two conditions associated together in the same patient, nor have I ever seen hyperplasia as a forerunner to cancer."

A number of authors (Meyer, Schröder, Taylor) have reported cases in which adenocarcinoma had developed in uteri which were the seat of hyperplasia; and we had likewise occasionally observed this association without attaching great significance to it. Both these lesions are so common that it would seem strange if they did not occasionally coexist, and in the past we have felt that this factor of coincidence explained cases in which both lesions existed side by side, rather than any more fundamental relationship between the two.

The studies of Mack and others have seemed to indicate that the clinical severity of the symptoms with hyperplasia parallels the degree of proliferative activity. For example, the cases of "mild" hyperplasia in his 200 series of cases were often cured by curettage alone, while in the severe grades, recurrence of bleeding was the rule, with cure only by the induction of the menopause by x-ray or radium. More important, however, have been the occasional reports of cases in which areas of unquestioned carcinoma have been found developing in a hyperplastic endometrium. In 1923 Meyer described two cases in which islands of undoubted adenocarcinoma were found embedded in the hyperplastic endometrium, much like implanted ova, and in one of these a direct transition from the benign to the cancerous areas was demonstrable.

This author has consistently expressed the viewpoint that all gradations between frankly benign and obviously malignant lesions may be seen, though, like all others, he emphasizes the fact that in the vast majority of cases, hyperplasia presents no great difficulty of microscopic diagnosis because of the complete absence of any suspicious histologic malignancy. In a small group of cases, however, the problem is far more difficult. Lesions closely simulating cancer, and yet proved by their subsequent clinical course to be benign, may be encountered, and so may actual cancer, on the basis of both histologic and clinical criteria.

Even expert pathologists will disagree in the interpretation of a certain small proportion of cases; and a careful follow-up study of a large number of borderline cases which have received only very conservative treatment, usually nothing more than curettage, is necessary to justify the histologic assumption of nonmalignancy. After all, it is what happens to the patient who is untreated, or treated only by conservative measures not capable of curing cancer, that determines

whether or not a lesion is malignant. Viewed in this light malignancy is fundamentally a clinical and not a histologic attribute, although by years of correlative study pathologists have learned to recognize certain histologic criteria as going hand-in-hand with clinical malignancy.

Only a few follow-up studies of these borderline lesions have been made. In Meyer's laboratory Hintze has studied 24 cases diagnosed as benign, but presenting such marked glandular and epithelial changes that they would certainly be interpreted by many as indicative of cancer. Although the only operation carried out in these cases was diagnostic curettage, not one of them subsequently developed cancer, a flattering tribute to the diagnostic acumen characterizing this laboratory.

An excellent study of the relation of hyperplasia to adenocarcinoma was made in 1932 by Taylor, whose material included 85 cases of hyperplasia, 50 of cervical polyps, and 152 of adenocarcinoma. This author presented evidence, available chiefly from the adenocarcinoma cases, that hyperplasia may be a predisposing factor in the later development of cancer.

Within recent years, we have been more and more impressed with the fact that hyperplasia is not so devoid of harmful possibilities as we once thought; or, to put it more accurately, that the proliferative forces responsible for benign hyperplasia may predispose to the development of cancer. The more and more frequent finding of borderline pictures; the increasing observation of cases in which hyperplasia and adenocarcinoma coexist, with at times apparently gradual transition of one into the other; the occasional occurrence of a history of functional menopausal bleeding and hyperplasia in patients who later develop adenocarcinoma—all these must make us question the innocuousness of hyperplasia. A further incentive for the present investigation of the subject is given by the recent studies which indicate that certain estrogenic substances are carcinogenic, so that it would not be surprising, to say the least, if a lesion known to be due to an excessive and prolonged estrin stimulation might predispose to cancer even more than merely irritative lesions, to which such a predisposing rôle is rather generally ascribed.

This is not the place to discuss the characteristics of benign hyperplasia, which are familiar to all gynecologic pathologists. It should be stressed, however, that the histologic picture is not a constant one, and that the same underlying process is concerned whether the endometrium presents the "Swiss-cheese" pattern, or a pattern scarcely distinguishable from that of the normal-interval endometrium, or a markedly proliferative pattern characterized by adenomatous activity of the glands and stratification of the epithelium. The term hyperplasia, therefore, as we have many times stressed, is a rather loose and not an altogether satisfactory one; but it is now so well established that it would not be easy to dislodge it. The proper evaluation of the histologic variations of hyperplasia can be made only if one bears in minds that they represent merely the reaction of the endometrium to varying degrees of estrin stimulation, and that there is an insensible

gradation from the normal proliferative or interval type of endometrium, to the so-called mild hyperplasia, then to the hyperplasia of frank "Swiss-cheese" pattern, and finally to the markedly proliferative hyperplasia pictures which may even closely resemble cancer.

The question then naturally suggests itself as to whether the next step might not be into the domain of actual cancer. As already stated, this possibility does not seem so remote in view of the newer work on the relation of endocrines, and especially the estrogenic substances, to cancer. The old dictum that a lesion is either cancer or not cancer may still be true; but there are many histologic intergrades which often make the decision difficult or impossible, though it cannot be assumed that in such cases we are actually witnessing a transition of benign into malignant disease.

As has been stated, the histologic picture characterizing hyperplasia of the endometrium, varied though it is, is not in any way suggestive of malignancy except in a very small proportion of cases. On the other hand, it is not so rare to find moderate degrees of proliferative overactivity, and it is possible, in the study of any large group, to demonstrate a definite gradation of changes from the frankly benign to the frankly malignant. Indeed, in one and the same uterus, as we shall show, one may see what is apparently a transition from a very benign type of hyperplasia, to areas which must be classed as borderline, and then to what all pathologists would agree is actual cancer. This statement cannot be made of cancer in most other regions, in which the demarcation between the cancerous and noncancerous tissue is likely to be quite sharp. Nor, it should be added, is it by any means true of all cases of corporeal adenocarcinoma. Hence, the special interest of hyperplasia in relation to cancer, an interest doubled by its estrogenic etiology, and by the newly demonstrated relations between estrogenic and carcinogenic substances.

In the milder degrees of departure from the typical benign "Swiss-cheese" pattern so common in hyperplasia, one may find only an unusual degree of epithelial proliferative activity, evidenced by pseudostratification or actual stratification, most frequently in the smaller glands. The epithelial nuclei may be larger and may take a much heavier stain than normal, while the glands themselves may be closely placed, so that the questionable area stands out quite sharply from its surroundings. In other instances, it is the paler staining of the questionable area which, as in many cases of actual cancer, sets it out in relief to the surrounding tissue. Mitotic activity, so characteristic of hyperplasia in general, is of little value in the differential diagnosis between this condition and adenocarcinoma. Occasionally, as in Fig. 4, the epithelium of the glands may exhibit what is apparently a definitely metaplastic change, so that it resembles quite perfectly the

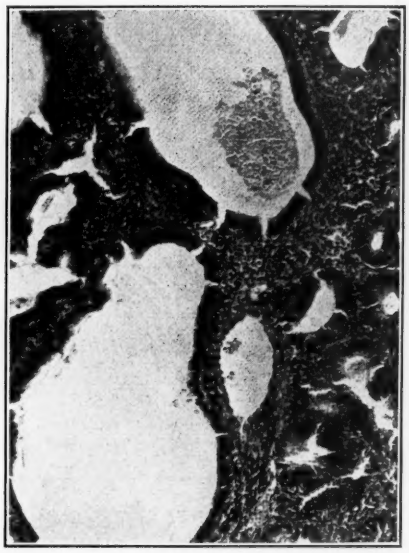

Fig. 1.

Fig. 2.

Fig. 1.—(Gyn. Path. No. 33193.) Showing mild proliferative activity in some of the smaller glands, with no suggestion of malignancy. Patient, aged forty-five years, had had persistent bleeding for four months.

Fig. 2.—(Gyn. Path. No. 41075.) Adenoma-like area in a case of benign hyperplasia. Patient, aged forty-one years, had had menorrhagia and metrorrhagia for one year.

Fig. 3.

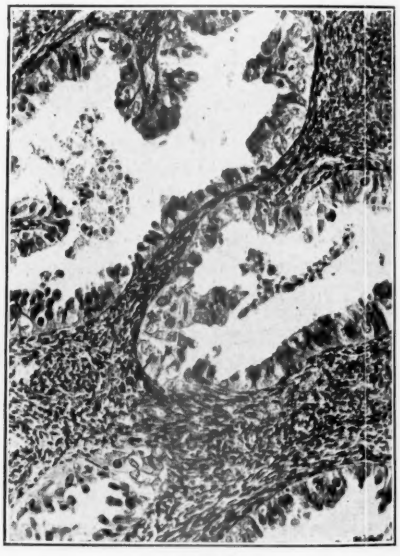

Fig. 4.

Fig. 3.—(Gyn. Path. No. 36587.) Markedly atypical gland pattern in benign hyperplasia. Patient, aged fifty years, was curetted five and a half years ago, and has remained perfectly well with no other treatment.

Fig. 4.—(Gyn. Path. No. 34478.) Such an area as this, which by its paler staining and the unusual epithelial changes, stands out from the surrounding tissue, might well lead to the suspicion of cancer. The epithelium in many places resembles that of the tube.

epithelium of the fallopian tube. The occurrence and significance of this metaplasia have been discussed in a previous paper by one of us (Novak).

In other cases, the glands themselves may show marked increase in number, with almost no interglandular tissue, and perhaps with very atypical convolutions and involutions. It is easy to see how such a picture, coupled with such epithelial overactivity as has been described in the preceding paragraph, must make the pathologist pause, and how one not familiar with the vagaries of hyperplasia might suspect adenocarcinoma. As a matter of fact, even expert pathologists will disagree in the interpretation of certain cases.

Since these perplexing problems most frequently arise in the diagnosis of uterine scrapings obtained by diagnostic curettage, their momentous bearing upon the patients' welfare is obvious, with a therapeutic decision to be made between simple radiotherapy and radical operation. No wonder, therefore, that in the occasional case the decision will be that of an eminent foreign gynecologist, also an excellent pathologist, who, on examining such a doubtful section in our laboratory during a recent visit, gave as his verdict, "Nicht Karzinom, aber besser heraus."

In only 13 of our patients during the reproductive epoch have we encountered such noteworthy evidences of proliferative activity as to raise the question of possible malignancy, though in all of these the changes involved only localized areas. The examination of the histologic context and the clinical histories of the patients made the exclusion of cancer reasonably easy and safe, and in no case was this diagnosis belied by the subsequent history. It will be seen, therefore, that in only a very small percentage of cases (1.3 per cent in our series) does the common hyperplasia *of the reproductive epoch* present pictures which might lead to the suspicion of cancer. The vast majority of cases are, from a histologic standpoint, very frankly benign.

Aside from such cancer-like areas as have been described, we have been interested in a rather curious epithelial reaction which we have noted in two of our cases. This is illustrated in Figs. 5 and 6. This epithelial change, which is seen only in scattered areas, is characterized by marked stratification, with often a syncytial merging of the cells of either the surface or gland epithelium. The cells become large and often develop vacuoles which may become so large that by compression of surrounding cells they produce a pseudoglandular picture. The syncytial suggestion is accentuated by the fact that the basement membrane is blurred and appears at times to be completely lost. An interesting feature is the infiltration with many eosinophilic leucocytes, while mitosis may likewise be noted.

We have been all the more interested in this picture because of its exact similarity with that recently produced experimentally by Migliavacca by injections of estrin into rats which had been previously cas-

trated. The effects produced upon the endometrium by employing this technic were interpreted by Migliavacca as due, not alone to estrin, but also to the prolan A normally found in castrated animals. In other

Fig. 5.

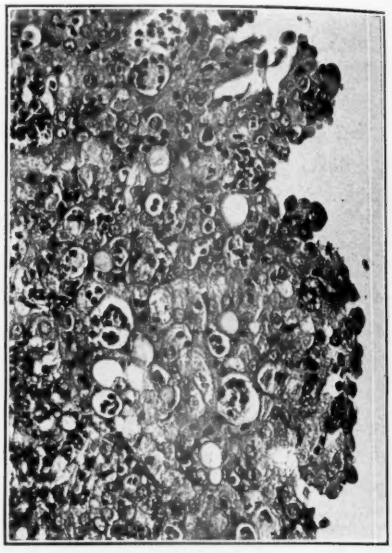

Fig. 6.

Fig. 5.—(Gyn. Path. No. 41075.) An area of peculiar "syncytial" proliferation of epithelium in the same case of hyperplasia from which Fig. 2 is taken.

Fig. 6.—(Gyn. Path. 37089.) Another syncytium-like picture, with somewhat higher power than that used in Fig. 5, from a patient of fifty-five years who had had irregular bleeding for five months. Other parts of the section show typical benign hyperplasia, and she has remained well after curettage five years ago.

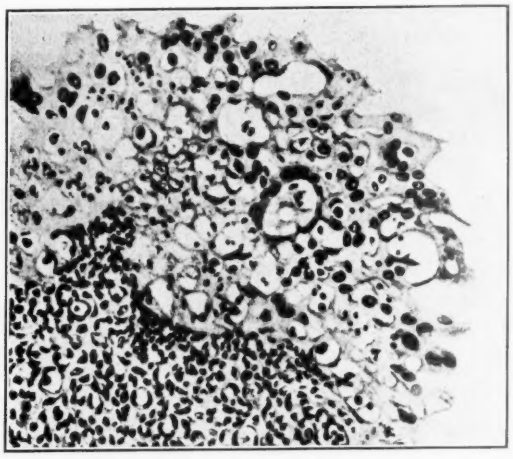

Fig. 7.—Syncytium-like epithelial proliferation produced by estrin injections into castrated rabbits (combined effect of estrin and Prolan A?). (Migliavacca.) Compare with Figs. 5 and 6.

words, he feels that these syncytium-like epithelial changes are to be explained as due to the combined action of these two hormone principles; and it is possible that the same explanation may apply to the

closely similar changes seen in our two cases. We had never previously observed such epithelial changes, and, so far as we know, they have not previously been noted in the human endometrium. Just why they should have manifested themselves in these two cases we do not know, as there seem to be no distinctive features in the histories of these two patients.

Another interesting epithelial change which we have encountered in six of our cases is the so-called squamous metaplasia. This is a relatively infrequent finding, though it has been described by a number of authors (Polano, Engelhorn, Novak). It may involve either the surface epithelium or that of the glands, more commonly the latter.

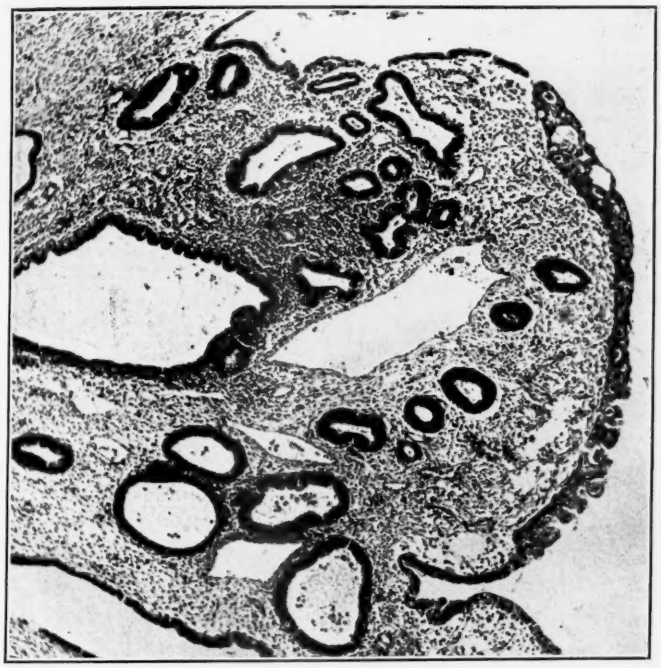

Fig. 8.—(Gyn. Path. No. 33712.) Squamous metaplasia of surface epithelium in a case of hyperplasia. Similar metaplastic changes were found in the gland epithelium of the same case. Patient aged twenty-eight years.

Meyer states that most characteristically the squamous nests project into the gland lumen in a glomerulus-like fashion. This is well illustrated in one of our cases (Fig. 8). Frequently, too, where the hyperplastic endometrium invades the musculature, the metaplastic changes are quite striking in the invading glands, producing complex patterns which may well lead to the suspicion of malignancy (Fig. 9).

There has been much discussion as to the mechanism of this squamous "metaplasia" since the first description of the condition by Ruge and Veit, as far back as 1882. It is seen in most extensive degree in association with the form of endometrial cancer designated as adenocan-

croid or adenoacanthoma; and there has been considerable discussion as to whether the cancer arises from a double matrix (''Doppeltumor''

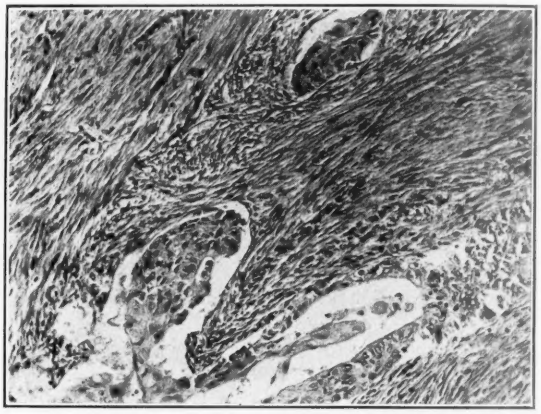

Fig. 9.—(Gyn. Path. No. 32156.) Squamous cell metaplasia in the glands penetrating the uterine musculature, the mucosa generally showing frankly benign hyperplasia.

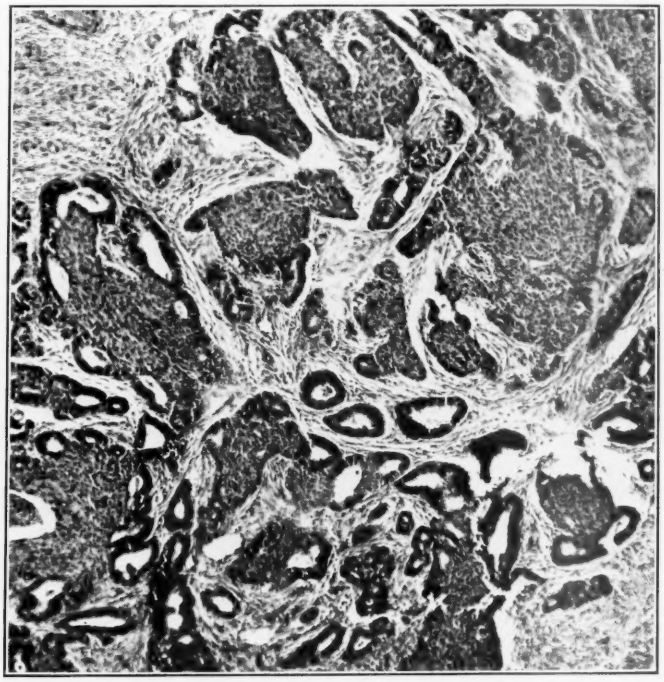

Fig. 10.—Extensive squamous metaplasia associated with adenocarcinoma, the interglandular squamous epithelium showing no histological evidence of malignancy.

or ''Collisionstumor''), or whether the squamous transformation is a later development in an adenocarcinoma. The latter viewpoint is the one which seems to have achieved the widest acceptance. Usually the

squamous epithelial growth is a benign concomitant of the malignant cylindric-cell carcinoma, but it may at times assume malignant characteristics of its own. The squamous epithelium probably arises from undifferentiated cells beneath the cylindric epithelium, cells which, under appropriate stimulation, may develop into squamous epithelium.

The most remarkable instance of this metaplastic change which we have observed is illustrated in Fig. 10, from a case of adenocarcinoma. In this section the squamous metaplastic areas have practically replaced the stroma and in many places seem to be compressing the gland structures. In this unusual picture the interglandular squamous epithelium shows no histologic evidence of malignancy, though it would seem that its obviously active growth propensities would make the step toward actual cancer a rather short one.

A special word seems necessary as to the striking pseudomalignant proliferative changes which one not infrequently sees in the polyps which so often are seen in cases of hyperplasia. This applies more particularly to the multiple polyposis of marked hyperplasia rather than to the single polyps of stationary hyperplasia pattern which may be found even when the endometrium as a whole is of the normal functioning type. The latter represent one type of so-called localized hyperplasia, corresponding to the localized areas of hyperplasia or "unripe endometrium" which may be found at various levels in the endometrium proper.

In a paper published by Novak and Martzloff from this laboratory some years ago (1924), attention was called to the fact that in polypoid hyperplasia the glands in the polyps may be so closely packed, and proliferative changes so marked, as to simulate adenocarcinoma very closely. Indeed, if such changes were seen in the endometrium proper, this diagnosis would no doubt be made by many pathologists; and yet their significance in polyps is much less. Actual carcinomatous changes can of course occur in uterine polyps, but they are relatively rare. Of the cases which have been reported, some at least are cases of polypoid carcinoma, for adenocarcinoma occasionally begins in just this polypoid form. It is especially this type in which, in a considerable number of reported cases, complete removal has apparently been accomplished by the curette, the microscopic examination of the uterus after removal showing no evidence of cancer. The examination of the pedicle is of great importance in deciding whether one is dealing with a polypoid cancer or a benign polyp which has undergone malignant change. The latter assumption is justified if there is no trace of cancer in the pedicle.

While this paper is primarily concerned with the gradations of epithelial proliferation seen in hyperplasia and adenocarcinoma, it is of interest to note that in an occasional instance it is the stromal elements which appear to bear the brunt of the proliferative forces at play in hyperplasia, and that in its most extreme form apparently tend to

the development of actual sarcoma of endometrial origin. The most striking instance of this kind which we have observed occurred in a patient of twenty-eight, who had had two curettements for persistent uterine bleeding, the scrapings showing typical hyperplasia, with also areas of epidermization, as shown in Fig. 8. The endometrium in the last curetting showed rather striking stromal activity, with an unusual number of mitoses and at least some nuclear hyperchromatosis. One year later she died in another city, and autopsy tissue which was received in our laboratory showed indubitable and extensive sarcoma of the endometrium.

One of the most surprising developments of this study is the finding of what is apparently a perfectly typical and actively growing hyperplasia in women often far beyond the menopause. The general view has always been that hyperplasia is a disease of reproductive life, though it may be observed for at least a short time after the actual cessation of menstrual function, in conformity with the existence of hyperestrinism during the earlier phases of the menopause (Zondek). Without having made any chronologic studies on this point, we ourselves have in past years thought it unlikely that hyperplasia could persist for more than a year or two after the cessation of menstruation, except in relatively rare cases in which a granulosa-cell tumor of the ovary is present.

And yet, in the study of this large material, we have found no less than 40 cases in which typical hyperplasia is found present in women from one to twenty-four years after the last menstrual period. In 32 of these 40 cases in which the data as to age are accurate, more than one year had elapsed since the menopause (two years in 4, three years in 2, four years in 2, 7 years in 4, eight years in 1, nine years in 2, ten years in 2, fifteen years in 3, sixteen years in 4, eighteen years in 1, nineteen years in 2, twenty years in 1, twenty-two years in 3, and twenty-four years in 1). In the remaining 8 cases, the patients were within one year of the menopause.

The histologic diagnosis in these cases we believe to be unimpeachable. It was of course not made on the mere basis of such features as large, cystic glands, as these are quite common in the senile endometrium. But when one finds the typical "swiss-cheese" pattern, with active epithelial growth, and an abundance of dense stroma not distinguishable from that of the reproductive phase, no other histologic diagnosis is possible. We are confident that if the age of the patient were not known, such a picture as that represented in Fig. 11, representing the endometrium of a woman of seventy-five years, would at once be diagnosed by every pathologist as typical hyperplasia.

The fact that hyperplasia may thus be found in women long after the menopause lessens the significance of this lesion in relation to granulosa-cell ovarian carcinoma of elderly women, in whom this ovarian tumor, as is well known, rather characteristically brings about an apparent

reestablishment of menstrual bleeding. Examination of the uterine mucosa in such cases usually reveals hyperplasia. Both the bleeding and the hyperplasia are explainable as due to the estrin produced by the ovarian tumor, so that it has commonly been accepted that the finding of well-marked hyperplasia in postmenopausal women should make one suspicious of granulosa-cell carcinoma. This is still true, but, unless one can also palpate an ovarian tumor, one is certainly not justified in assuming that a small nonpalpable granulosa-cell carcinoma probably exists, as some of us formerly believed.

It has been quite clearly established, both in the human being and in the experimental animal, that the immediate cause of hyperplasia is an excessive stimulation with estrin, underlying which is an overactivity of the follicle-ripening gonadotropic hormone of the anterior hypophyseal lobe. What, then, is the source of the estrin in this late post-

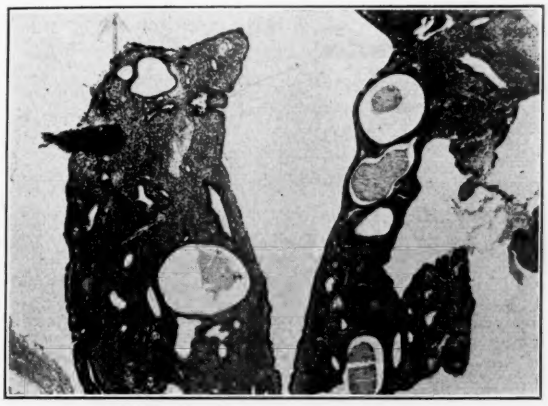

Fig. 11.—(Gyn. Path. No. 41389.) Benign hyperplasia from a patient of seventy-five years, twenty years after the menopause. There had been sudden profuse bleeding beginning four days before admission.

menopausal or senile phase of life, long after cessation of ovarian secretory activity? That the ovaries have actually become functionless receives histologic support in 19 of our cases in which they are available for study. They present the typical senile structure, with no sign of follicular activity and in some cases with practically complete disappearance of all follicular structures. Estrin has been found in the urine of women long after the menopause, though no intensive studies on this point appear to have been made. It is difficult to believe that the source of the hormone can be the senile ovary, and it seems more likely that some other structure, possibly the anterior pituitary lobe, may assume an estrogenic function when the ovary steps out of this rôle. We expect to be able, by hormone studies now being projected in our laboratory, to throw some light on this question of estrin production in old women, and perhaps thus on the occasional occurrence of hyperplasia in postmenopausal life.

Frank has, in several publications, mentioned finding the estrogenic factor in the urine of women after the menopause, although he does not discuss the source of the hormone in these cases. Especially suggestive, however, is the recent paper by Frank, Goldberger and Salmon, in which report is made of the finding of the estrogenic factor in the urine of surgically castrated women. This would at once seem to indicate that the ovaries are not the producing source, a view coinciding with our own impressions, based on the less decisive histologic studies we have been able to make of the ovaries of women with postmenopausal hyperplasia.

In a recent study of 130 cases of postmenopausal bleeding, all in women over forty-five who had had complete amenorrhea for from one year to twenty-five years, Breipohl reports the finding of a proliferative endometrium in 13, hyperplasia in 15 (this including 2 in which there was a granulosal tumor of the ovary), secretory endometrium in 3. In other words, in 31 of 130 bleeding cases, almost 25 per cent, the endometrium exhibited evidence of undoubted activity, though menstruation had ceased long before. Nearly half of this group was made up of cases of hyperplasia, which in one case was observed as late as twenty-five years after the menopause. As no studies of the ovaries were made, his assumption of persisting ovarian function in such cases is not justified; and we believe this very improbable, on the basis of our own histologic studies.

The few studies which have been made on the physiologic status of the senile ovary are inconclusive and contradictory. It has generally been accepted, as W. Waldeyer stated sixty-five years ago (1870), that complete atrophy of the follicular structures occurs within a few years of the menopause. In the case of experimental animals physiologists have been able by hypophyseal implants to reestablish ovarian function; but there is much doubt whether in the human being such a result can be accomplished by any available method of administration of anterior pituitary or anterior pituitary-like gonadotrophic principles. Only Westman has reported the finding of corpora lutea in the ovaries of 2 postmenopausal women who had received injections of pregnancy blood, but his conclusions are not generally accepted by other workers (L. Waldeyer). Tschertok and Penkow report negative results in 7 cases in which somewhat similar studies were made, though in these, pregnancy urine was used for the preoperative injections.

It seems clear, nevertheless, that after the menopause, the functional activity of the ovary may persist for a time, especially so far as the production of estrin is concerned. This is comparable to the prepubertal development of follicles and production of estrin, followed later by anovulatory and still later by ovulatory cycles, which so often characterizes the inauguration of menstrual function at puberty. Just how long after the menopause this estrin-producing capacity may persist, however, is a problem which only future histologic and endocrinologic studies can settle.

COEXISTENCE OF HYPERPLASIA AND ADENOCARCINOMA

The most provocative aspect of our study, however, has emanated from the examination of 104 cases of actual adenocarcinoma, because in a surprisingly large proportion the uninvolved endometrium shows definite hyperplasia, while in other cases there is a history of menopausal bleeding strongly suggesting hyperplasia at that epoch, a suspicion which in 4 cases can be proved because the tissue from curettings done at that time has been available for study. Moreover, in 5 others there was a history of one or more curettements done elsewhere at about the menopausal age, presumably for functional bleeding, though the slides could not be secured. In 6 other patients there was a definite history of menopausal flooding, though no operation had been done at that time.

When we use the term "hyperplasia" in connection with this group of cases, it should be made plain that we do so in the very broad sense in which it has come to be employed, i.e., as indicating the picture which is considered to be due to excessive estrin stimulation. As already stated, the diagnosis of this condition in women of reproductive age is often colored by the clinical history of bleeding, while the chief histologic criterion available to us, aside from absence of secretory activity, is a varying degree of proliferative activity, whether it be an unusual development of the epithelium of the smaller glands, abundance of stroma, or cystic distention of some of the glands, with possibly a "Swiss-cheese" pattern. It is in this sense that we have used the term here, for the problem with which we are concerned is not so much the relation to cancer of full-blown hyperplasia as of those proliferative conditions which may be considered to be of estrogenic origin.

The typical mucosa of women well beyond the menopause is thin and atrophic, with fibrotic stroma, and with occasional and usually moderately dilated glands. This, at any rate, is the kind of endometrium we expect to find after ablation of the ovaries in either the human being or the lower animals. When an infection of such an endometrium occurs, as in senile endometritis, the cystic distention of glands is more pronounced, and the distended glands often contain cell-detritus or leucocytes, instead of being empty or containing the clear albuminoid transudate which is so common in either the normal or the hyperplastic endometrium. In fact, it would seem logical to believe that this transudate, if such it be, is evidence of increased hyperemia and possibly of excessive estrin stimulation, a view supported by the fact that when this albuminoid content is conspicuous in senile endometria, one can usually find other evidences of proliferative activity, such as a thickened proliferative type of gland epithelium in the smaller glands or a very active looking stroma. To put it another way, many of the various grades of so-called senile endometrium show evidence of a hang-over or persistence of estrin activity.

It is our impression that in the senile endometrium, as in that of the reproductive epoch, one can distinguish all grades of estrin effect. At one extreme is the very atrophic type in which the estrin effect is apparently in complete abeyance, at the other the genuine hyperplasia of hyperestrinism, with various intergrades between these two extremes. This observation checks up with the reports which are now being made in increasing numbers as to the finding of estrin in both the blood and the urine of elderly women. The term "senile endometrium," therefore, is a chronologic rather than a histologic one, for it does not refer to any one characteristic histologic picture. Paradoxical as it may seem, it will embrace even some cases of hyperplasia.

It need not be emphasized that difficulties of histologic evaluation are at times encountered, especially if numerous cystic glands are observed, so that a "Swiss-cheese" gland pattern may be simulated in an endometrium which is not hyperplastic. Even in the hyperplasia of reproductive life, it is quite common to find flattening of the epithelium of the larger cystic glands, while on the other hand, one may see very active epithelium in some of the cystic glands of the senile endometrium. In either the senile or the hyperplastic endometrium, the gland lumina are either empty or they contain an eosin-staining albuminoid fluid, the significance of which no one knows, but which is quite certainly not a retention product, for it is often found in endometria which show no gland distention whatsoever.

When, therefore, evidence of such proliferative activity has been pronounced, we have included the cases in this group of hyperplasia coexisting with carcinoma, though in the great majority the endometrial pattern was of the "Swiss-cheese" type characterizing the frank variety of hyperplasia. In all such interpretations, as in the diagnosis of hyperplasia in cases of functional bleeding, we are faced with the difficulty of trying to interpret physiologic abnormality on the basis of histologic change, but we believe our criteria have been those commonly accepted.

Not only do adenocarcinoma and hyperplasia frequently coexist, but in many instances one can see in one and the same case, and perhaps in one and the same section, all grades of transition from frankly benign, to borderline, to obviously malignant histological pictures. Altogether we have studied 104 cases of corporeal adenocarcinoma, and in fully 25 of these (24.03 per cent), we have found a coexisting hyperplasia of the endometrium. The significance of this figure is increased when we bear in mind that in 40 of our cases, sections through noncancerous mucosa were not available for study. Of the 64 cases in which both cancerous and noncancerous mucosa were available for study, fully 39.06 per cent showed hyperplasia, an incidence which to us was most astonishing. In case after case we find pictures like those shown in Figs. 12, 13, 14, and 15, showing the two lesions side by side. In some, like Fig. 12, one can trace the transition by definite gradations from benign hyperplasia,

to a proliferative borderline stage, merging almost insensibly into out-and-out cancer. It is therefore in these cases of postmenopausal hyperplasia rather than in those far more commonly seen in the reproductive epoch that some sort of relationship to cancer seems clearly established.

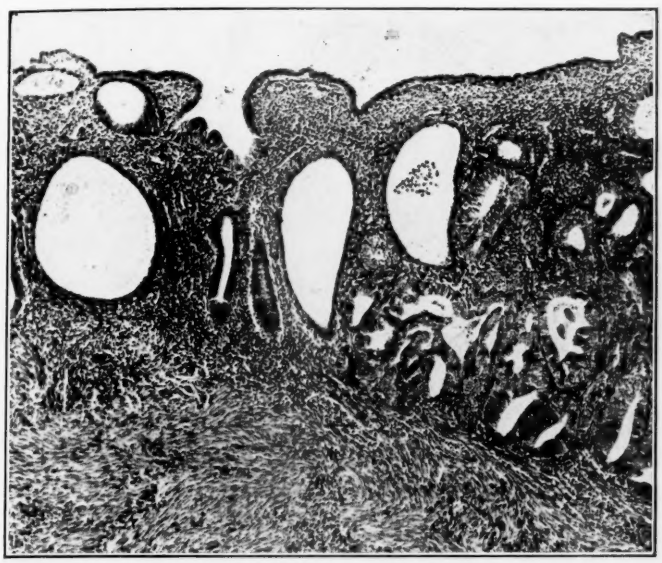

Fig. 12.—Benign hyperplasia on the left, passing on to markedly proliferative pattern on the right, beyond which (though not shown in the picture) was a definite adenocarcinoma.

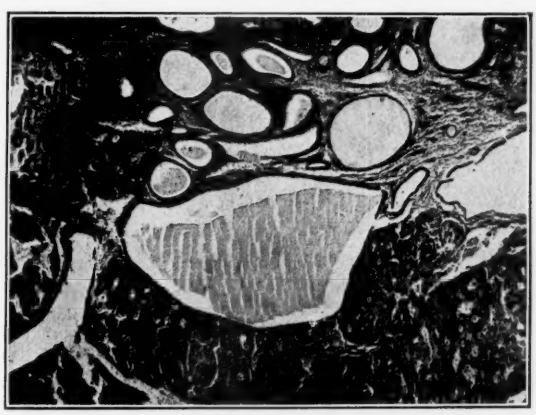

Fig. 13.—(Gyn. Path. No. 39555.) Typical benign hyperplasia below, adjoining equally typical adenocarcinoma above. Patient aged fifty-nine years.

It is of interest to compare the incidence of hyperplasia in normal women well beyond the menopause with hyperplasia in the women with adenocarcinoma in the same age group. The age of fifty-five years was arbitrarily selected as the basis for this comparison. Of 804 cases of hyperplasia with accurate data as to the age, 40 occurred in women

beyond fifty-five, an incidence of 4.8 per cent. On the other hand, 61 of our 104 adenocarcinoma patients were beyond fifty-five, and 13 of these showed an associated hyperplasia, an incidence of 21.3 per cent. It is probable that this figure would be much higher were noncancerous endometrium available for study in all of our cases. In 40 of our cases, as already stated, there was no such tissue for study. Even when it was, it was usually only the endometrium immediately adjoining the cancer area.

The suggestion arising from the above comparison would be that there must be some relationship between this disproportionally high incidence of hyperplasia in the cancer cases and the development of cancer. What this relationship is no one can say in the present state of our knowledge,

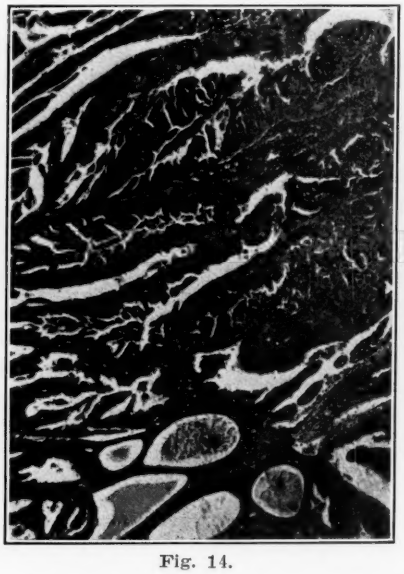

Fig. 14.

Fig. 15.

Fig. 14.—(Gyn. Path. No. 36910.) Coexisting hyperplasia (at bottom) and adenocarcinoma, in patient of fifty-nine years.

Fig. 15.—(Gyn. Path. No. 38689.) Below and to left is seen a typical hyperplasia pattern, while above and to the right is seen adenocarcinoma. Patient aged sixty-two years.

though various possibilities can be thought of. Does a hyperplasia persisting after the menopause predispose to the development of cancer? This would seem to be the case, and, since the only known cause of hyperplasia is a persisting hyperestrinism, the natural assumption would be that it is this factor of abnormally long-continued subjection of the endometrium to estrin stimulation which is the important predisposing influence. Crossen and Hobbs have recently reported a statistical study of the menopausal ages of women with adenocarcinoma, indicating a high incidence of late menopause in such cases. It seems likely that hyperplasia and its causative hyperestrinism must have been factors in the delayed menopause.

We feel quite conservative in using the term, "predisposing," as regards the relation of hyperplasia to adenocarcinoma, for there are many who now look upon estrogenic substances as actually carcinogenic. The studies of Lacassagne, Overholser and Allen, Hofbauer, Cori, and others, all revolve about this concept. We shall not review the evidence along this line, for this constitutes a story in itself; but a few especially pertinent observations may be noted. Lacassagne was able to produce mammary cancer by theelin injections in male rats of a species in which the males are relatively immune to spontaneous mammary cancer. On the other hand, Cori's experiments have shown that the very early castration of mice, of a strain with notoriously high cancer incidence, confers immunity to cancer. Large amounts of estrin have been found in the blood of both male and female cancer patients (Dingemanse, Freud, de Jongh and Laqueur), while the follicle-stimulating principle of the anterior hypophysis has been found in the urine of 81.8 per cent of women suffering with various forms of genital cancer (Zondek). Schön has not only confirmed the finding of estrin in women with genital cancer, but she has found that the hormone disappears from the urine after complete removal of the cancer, to reappear again if recurrence of the tumor takes place. At times, however, estrin is not found with even extensive cancer.

This question is fascinatingly bound up with the newer investigations as to the chemistry of the sex hormones, and as to the close chemical kinship of the latter with certain well-known nonhormonal substances which are known to be carcinogenic as well as estrogenic. To this group belong certain sterol derivatives, tar, the bile-acids, and certain vitamins. Some of this newer work has been discussed in a recent paper by Novak; it has been much more fully reviewed in a recent publication by Leo Loeb. The latter states, as regards the above-mentioned experiments with mammary cancer, that "it may be regarded as established that estrogenic substances, as a rule acting in association with hereditary factors, may be strongly carcinogenic; but such carcinogenic action is restricted to the tissues of the mammary gland with which they combine and in which, under normal conditions, they induce growth processes."

Especially pertinent to our present problem is the fact, as emphasized by Loeb, that the cancer produced by estrogenic substances, as well as that produced by the tar hydrocarbons, is preceded by a preparatory stage, beyond which cancer follows even though the carcinogenic factor ceases to operate. The changes produced are gradual. In the case of the tar hydrocarbons, and presumably also with the estrogenic hormones, there is a capacity "to induce the transformation of normal into cancer tissues at any point in which they come into long-continued contact with tissues, whether they are of epithelial or of connective tissue origin, provided they still possess the potentiality to grow and proliferate."

Here, then, on the basis of sound experimental work, we apparently have an explanation, not only of the carcinogenic possibilities of the hyperestrinism which underlies the occurrence of hyperplasia, but also of the frequency with which one encounters gradations of proliferative activity which represent, as it were, stepping-stones to cancer. It thus seems not inappropriate, in so far as the endometrium is concerned, to speak of actual transitions to cancer, a phrase ordinarily shunned by general pathologists, and perhaps quite properly so as regards cancer in general.

Another hypothesis which suggests itself in explanation of the frequent finding of hyperplasia in cancer long after the menopause is that perhaps the carcinoma itself acts as the estrogenic factor and is thus responsible for the production of the hyperplasia pattern in the endometrium. This explanation seems less tenable than the one already discussed, chiefly because of the not rare finding of hyperplasia in postmenopausal women who do not have cancer. While certain carcinogenic substances are also estrogenic, there is no evidence that cancer itself is. It is possible that both the hyperplasia and the carcinoma may be due to an increased or perverted function of some endocrine organ, whether this be the pituitary or some other gland, which is responsible for the production of estrin in old women; though this explanation is also entirely hypothetical. An abundance of experimental work, some of which has already been quoted, indicates that prolonged and excessive estrin stimulation may predispose to or induce cancer, so that this order of events, rather than the reverse, would seem likely as regards the relation of hyperplasia and cancer. Finally, although there is no direct evidence on this point, one must at least think of the possibility that an estrogenic effect in old women may be of chemical rather than purely hormonal nature, possibly as a result of some metabolic change involving the sterol substances which have been shown to be estrogenic.

SUMMARY

The evidence presented in this paper points to a relationship of some sort between hyperplasia of the endometrium and corporeal adenocarcinoma. The material studied includes 804 cases of hyperplasia and 104 of adenocarcinoma, encountered in a review of 12,813 cases passing through our laboratory during an eleven-year period (Jan. 1, 1925, to Jan. 1, 1936). While in the overwhelming majority of cases hyperplasia is a very frankly benign lesion, a small minority (14 of our 804) reveals evidences of marked proliferative tendencies which may even simulate cancer.

The histologic characteristics of benign hyperplasia present degrees and variations which are discussed in the paper, as are the proliferative and pseudomalignant pictures at times encountered (stratification, adenomatous proliferation, marked atypicalness of glands, syncytium-

like epithelial proliferation, squamous metaplasia of gland or surface epithelium, etc.). Atypical gland proliferations, simulating adenocarcinoma, are especially frequent in the polyps so often seen with hyperplasia.

An interesting finding in this study was that hyperplasia is not rare in women long after the menopause (40 of 804 cases); and the etiology and significance of this are discussed. The occasional occurrence of hyperplasia with bleeding in elderly women lessens the significance of these findings as pointing to the probability of granulosa-cell carcinoma of the ovary, unless an ovarian tumor can actually be palpated.

In the study of the 104 cases of adenocarcinoma, the most impressive result was the demonstration of a coexisting hyperplasia and adenocarcinoma in fully 25 of the cases in which some of the noncancerous endometrium was available for study. Since the great majority of the adenocarcinoma cases (78 of 92 in which we have accurate age data) were beyond the menopausal age, this at once suggests that a postmenopausal hyperplasia, or, perhaps more accurately, the endocrine dysfunction responsible for it, must strongly predispose to the development of adenocarcinoma. Since a persistence and relative excess of estrin is accepted as the cause of hyperplasia, it would seem that it is this endocrine factor which must be suspected as the one predisposing to cancer genesis.

It should be emphasized that the ordinary hyperplasia of the reproductive epoch is not only frankly benign from the histologic standpoint, but also that it has no apparent predisposing influence in the causation of adenocarcinoma during menstrual life. It would seem from our studies that it is the postmenopausal persistence of hyperplasia which is in some way bound up with the occurrence of the common postmenopausal type of adenocarcinoma.

The question of the relation between estrogenic and carcinogenic substances, and the carcinogenic properties of estrogenic substances, is discussed in our paper. Whether the persisting estrin stimulation in cases of postmenopausal hyperplasia serves merely to keep up a form of chronic irritation, or whether its carcinogenic effects are more direct and fundamental, cannot be answered as yet, though the latter seems, in the light of recent experimental work, to be the more likely explanation. In our own cases of coexisting hyperplasia and adenocarcinoma, we have in some been able to show a definite transition of the benign to a borderline and then to an undoubtedly malignant pattern: so that, in the endometrium at least, it would seem that we are dealing with histologic intergrades between benign and malignant lesions. When such pictures are encountered in the endometrium obtained by diagnostic curettage, there is often a justification for the dictum, "Nicht Karzinom, aber besser heraus."

Since, on the basis of these observations, hyperplasia is to be classed as a precancerous lesion, in the sense of one predisposing to later adenocarcinoma, it would at first thought seem that we should all the more generally recommend abolition of ovarian function by x-ray or radium in the treatment of functional bleeding of the menopause. Whether or not this would be of any practical value, however, is questionable since it seems quite certain that other sources of estrogenic substance than the ovary must be reckoned with.

One must be struck with the analogy of this problem to that of the breast, in which likewise the ovarian hormones can produce either very benign forms of cystic mastitis, or more markedly proliferative pictures which are scarcely or not at all distinguishable from cancer. In still another field, the cervix, we are now finding similarly puzzling borderline pictures, though we know almost nothing about their possible endocrine relationships. We refer particularly to leucoplakia and, even more, to the intraepithelial carcinoma or Bowen's disease, in which the epithelial layer presents all the characteristics of cancer except for invasiveness, and which are quite similar in appearance to the growing margin of an actual cancer. Are such lesions in themselves benign, as would seem to be indicated by the fact that they have often been cured by the most conservative procedures? Or are they inevitable precursors or very early stages of cancer, which, as in Bowen's disease of the skin, may not develop invasiveness and other malignant characteristics until the lapse of perhaps many years? Finally, may such lesions represent the response of the cervical epithelium to abnormal endocrine stimulation?

In all three of these fields, cervix uteri, corpus uteri, and breasts, we have to deal with the possible rôle of ovarian hormones. This seems significant in view of the growing opinion that the carcinogenic possibilities of estrogenic substances are most to be reckoned with in those organs in whose growth and activities estrin normally plays an important part.

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DISCUSSION

DR. RICHARD W. TELINDE, Baltimore, Md.—For several years there have been references to this subject in the literature, but the conclusions arrived at by the several authors vary markedly. Cullen, the first gynecologist to describe hyperplasia, concluded that it bore no relation to malignancy. In Burch's most recent paper he says, "I have never seen the two conditions together in the same patient nor have I seen hyperplasia as a forerunner to cancer." Fluhmann and Stephenson in a review of 22 cases of adenocarcinoma found no traces of hyperplasia associated with it. In 1923 Robert Meyer reported 4 cases of early carcinoma occurring in hyperplastic endometrium. He cautions his audience not to assume that this is a common occurrence for, to quote him, "These few cases . . . have come to light only after long years of collecting and investigating." In contrast to the conclusions reached by these men, Howard Taylor in 1932 presented evidence from which he concluded that "when the hyperplasia is at all marked, the possibility of a predisposition to the development of cancer should be considered and the case regarded with the same degree of suspicion now bestowed upon the diffuse form of hyperplasia of the breast epithelium." He presented two cases of carcinoma of the endometrium from his laboratory in which previous curettings had been diagnosed hyperplasia. But, he frankly states that on reexamination it was found that carcinoma had been overlooked in the original curettings.

And now Novak and Yui find the astonishing incidence of nearly 40 per cent of hyperplasia in the 64 cases in which both cancerous and noncancerous mucosa was available for study. How can we correlate these findings with those of Fluhmann, Burch and Meyer? It would seem that the most likely explanation is a difference in their interpretation of what constitutes the minimum histologic changes necessary to a diagnosis of hyperplasia. There are no absolute criteria for the diagnosis. I have had the opportunity of examining the material upon which Novak and Yui made this study, and, frankly, their histologic interpretation of hyperplasia is more liberal than mine.

In order to give myself a background for the study of these slides I first studied several nonmalignant postmenopausal endometria. A certain number of cystic glands are frequently encountered and the fact that they are almost invariably filled with a clear secretion and that the epithelium is almost always greatly thinned suggests to me that they are retention cysts. But there are some postmenopausal endometria in which the histologic picture is remarkably like that of premenopausal hyperplasia, but in my judgment they are relatively rare. Dr. Novak has shown that 4.8 per cent of his 804 cases of hyperplasia occurred after fifty-five years, but he did not give us what percentage of postmenopausal benign endometria showed this histologic pattern. In studying 20 postmenopausal endometria picked at random from our laboratory I found the same histologic picture which Novak and Yui have

interpreted as hyperplasia in 11 cases. This is an incidence of 55 per cent as compared with an incidence of 40 per cent in their carcinoma cases. This causes me to question its etiologic significance in the carcinoma group.

If hyperplasia is a precancerous lesion one would expect a parallelism between the age incidence of hyperplasia and carcinoma. The greatest incidence of hyperplasia is in the fifth decade of life. After fifty the incidence of hyperplasia decreases but the incidence of adenocarcinoma increases, so instead of a parallelism in their incidence there is a divergence. I have assured innumerable women in the late forties or early fifties who have had recurring bleeding due to hyperplasia that after getting past the menopause their chance of further trouble due to the hyperplasia would be nil. I have never had one of these women return with carcinoma of the endometrium. But even if an occasional one is later a victim of carcinoma, is it more than one might expect on the law of chance?

If we are to change our concept of hyperplasia from a purely benign lesion to a precancerous one, the next logical step is to modify our present conservative treatment in a radical direction. This I feel would be a mistake, and it is with the thought of preventing unnecessary radical surgery or radiation that I have brought up these objections to the acceptance of an attractive theory which does not coincide with my clinical or pathologic experience.

DR. FRED J. TAUSSIG, ST. LOUIS, MO.—We are at present engaged in an analysis of corpus cancer cases at our hospital and have found that of the patients operated upon, the average age was fifty-five. In general we were not impressed with the frequent occurrence of a late menopause. We were, however, struck with one peculiar thing, that there were 5 patients on whom a diagnostic curettement had been done with a microscopic report of hyperplasia. Vaginal hysterectomy was performed in spite of the negative findings and carcinoma was found in the uterus on removal. There were only three patients in our series in whom there was a definite history of a preexisting hyperplasia.

I have been particularly interested in the relationship between hyperplasia and adenocarcinoma in young individuals, since I have had two very striking instances suggesting a connection. In one patient, aged fifteen years, a curettement was done and a polyp was removed with resulting six months' amenorrhea. Then at the age of nineteen years with a return of the menorrhagia, curettement was again done and the sections were diagnosed as hyperplasia, but Dr. Otto Schwarz made this comment, "This case bears watching." Within a period of one year the bleeding returned and a large polypoid mass was found protruding at the external os about the size of a thumb. Biopsy showed definite and well-developed adenocarcinoma of the body of the uterus. The patient refused hysterectomy and she was given 3,675 mg. hours of radiation. Upon my insistence she returned four months later and curettement at that time showed no more cancer. Four years have now elapsed, and there has been no recurrence.

The other patient was brought to me at the age of thirteen because of prolonged and excessive bleeding, which yielded promptly to corpus luteum extract hypodermically. At the age of seventeen there was a recurrence and the same treatment was employed with success. Two years after this, at the age of nineteen, she returned with the same symptoms and all therapeutic measures failed. She also refused removal of the uterus and x-ray treatment served only to check the bleeding for two months, when it returned more profusely than ever. Finally curettement was done and the particles removed showed early adenocarcinoma. A supravaginal hysterectomy was done over five years ago, and there has been no recurrence.

DR. C. FREDERIC FLUHMANN, SAN FRANCISCO, CALIF.—Studies made possible by freely obtaining biopsy specimens of the endometrium, as well as blood estrin determinations, have shown that the problem of hyperplasia of the endometrium is not

a simple one and that we may distinguish two conditions which yield a common histologic picture in the endometrium but which differ greatly in their clinical manifestation and functional behavior.

In the first place, there is the condition of an active "hyperplasia endometrii," or the "metropathia hemorrhagica" of Schroeder. Histologically, the endometrium presents the appearance so well described by Novak of a dense stroma, large proliferating glands, cystic glands, large blood vessels, and with many mitotic figures denoting marked growth activity. Clinically, these patients have enlarged, softened uteri and are characterized by cyclic or irregular uterine bleeding. And finally, the blood estrin tests, as I pointed out last night, show *not* a constant high content of estrogenic substance, a "hyperestrinism," but a definite increase which is associated with the onset of the hemorrhage. In the intervals between the periods of bleeding the blood-estrin may give normal values or negative reactions. This type of hyperplasia I have never seen in patients in the postclimacteric period except accompanying certain tumors of the ovary.

On the other hand, biopsy specimens of the endometrium have shown that a histologic picture essentially indistinguishable from "hyperplasia endometrii" may occur under very different conditions. I have found it, for instance, in 12 patients with longer or shorter periods of amenorrhea. These women may show small atrophic uteri. They do not bleed, and blood-estrin tests give normal values or negative reactions. The condition may persist for months or years as repeated biopsies have shown. These patients may very well be said to have a "hyperplasia endometrii," but they do not present the same condition as those of the first group. The endometrium does not show the same intense growth activity, nor the presence of many mitotic figures. It is, so to speak, a "passive form," and although it can be demonstrated in the postclimacteric, in my experience it is comparatively rare. If this should be the condition that Novak refers to, it is indeed remarkable that this type, the so-called passive form, should be associated with malignancy, whereas in early life the active form with its intense cellular activity should be a relatively benign state.

And, finally, although the concentration of estrin in blood and urine rises during the postmenopausal period, it is in association with involutional changes in the uterus and vagina. If it were possible for it to stimulate a growth activity of the endometrium one would certainly anticipate abnormal uterine hemorrhages preceding the actual development of the carcinoma.

As Dr. Stephenson and I pointed out in a previous communication, a study of the material available in the Stanford Gynecological Laboratory does not suggest any relationship between hyperplasia and carcinoma except the possibility of their coexistence. It seems to me that one must accept with hesitation any theory which would make us regard hyperplasia endometrii as a "precancerous" condition.

DR. NOVAK (closing).—In the group of cases which I presented, of adenocarcinoma together with hyperplasia in the adjacent mucosa, I am frank to say that the matter of differentiation from senile endometrium did not at first occur to me, because the histologic picture seemed so different from that of the latter. After going over some of the sections with Dr. TeLinde, I added several paragraphs to our paper to emphasize why, in our opinion, these pictures could not be mistaken for simple senile endometria. In our own informal discussion, Dr. TeLinde laid great stress upon the fact that some of the glands show a flat epithelium and some show a pale-staining liquid or albuminoid exudate. Neither one of these objections seems to me valid.

In the perfectly typical hyperplasia of reproductive life, it is very common to find flattening of the epithelium in many of the cystic glands, while an albuminoid exudate is often seen not only in typical hyperplasia but also in the normal endome-

trium. Certainly it cannot be interpreted as a retention product, and I do not know of anyone who has so considered it. To illustrate these points, I am throwing on the screen a number of slides from Schröder's monograph, all showing typical hyperplasia, but showing also flattening of the epithelium of some of the large glands and also the albuminoid exudate under discussion. I am showing also, from the same author, a typical hyperplasia from a woman many years after the menopause.

Both of the discussants seem to me to have missed the chief point of the paper, since both speak of the lack of parallelism between the age incidence of hyperplasia and of adenocarcinoma. We tried to make it plain that the hyperplasia of menstruating life seems to have no relation with cancer, but that if the postmenopausal endometrium is subjected to persistent estrin stimulation, there is apparently a real predisposition to cancer. A chronic irritation may be of little importance in a young person, but may predispose to cancer in the older patient. And the same thing may be true of a persistent hormonal irritation.

Dr. Fluhmann speaks of two different varieties of hyperplasia, but we have not been able to make any such distinction in our laboratory. He suggests that the kind of hyperplasia we have found in these older patients is like that which one finds in amenorrhea. This seems strange, since it is rather generally accepted that these cases of "polyhormonal" amenorrhea in which hyperplasia is characteristically found are due to an excess of estrin stimulation.

To produce cancer there must admittedly be some unknown constitutional predisposition or dyscrasia, together with some local factor, most often chronic irritation. We believe that our work indicates that postmenopausal proliferative activity of the endometrium, due to an estrogenic stimulation of as yet unknown source, constitutes such a local predisposing factor, and that it is related to the development of a considerable fraction of our cases of adenocarcinoma of the corpus uteri.

Fauvet: The Genesis of Brenner Tumors, Arch. f. Gynäk. **159**: 585, 1935.

Fauvet describes four cases of Brenner tumors of the ovaries in detail. He does not believe that these tumors are comparable to endometrioses because they are always ovarian in origin while the endometrioses are not necessarily so. He is inclined to agree with Schiller that the Brenner tumor arises from the ovarian rete rather than with Walthardt's cell focus theory. He believes that they arise as a result of hypoovarianism rather than from hyperfunction of the ovary. An analogy is made with Behring's statement regarding hemorrhagic metropathy, chronic cystic mastopathy and endometriosis, namely that these are "paramenstruations" and result from dysfunction rather than from hyperfunction of the ovaries. He believes further, that there exists a connection between these tumors and the adrenals although he is unable to prove this.

RALPH A. REIS.

Chi, Li, and Yang: The Presence of Carotin in Ovarian Tumors, Chinese M. J. **49**: 751, 1935.

The authors describe a case of dermoid cyst of the ovary, combined with pseudomucinous cystadenoma, which had spontaneously ruptured and resulted in extensive peritoneal implantations. This condition is generally known as pseudomyxoma peritonei. The fluid contents of such tumors may be colorless or brownish; the latter color is probably due to the presence of altered blood pigment. In the author's case carotin pigment was present in large quantities. The patient also had a high content of carotin in the blood.

C. O. MALAND.

SECONDARY SEQUELAE AFTER INTERPOSITION OF THE UTERUS

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(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)

BETWEEN the years 1914 and 1918, in a special clinic for cystoscopy of the female, some forty patients with bladder complaints, who had been subjected to interposition operations by others, came under observation. At that time the indications for the operation were not clearly defined and the technic had not been perfected. Occasional instances of unsatisfactory results encountered thereafter, as well as the recollection of the first group of cases, discouraged the use of this operation for several years, until a careful consideration of the technical details convinced me that the undesirable sequelae could be eliminated. Mackenrodt, Dührssen, Watkins, Wertheim, Schauta, and others have contributed to the present-day technic, which probably varies somewhat in different clinics. For the past ten years I have done the operation in selected cases of procidentia and large cystocele with considerable satisfaction and without the embarrassment of subsequent therapeutic problems. This has been due to restricting its application absolutely to women past the menopause, as well as to a proper regard for certain precautions which suggested themselves, as the causes of unpleasant end-results were analyzed. The purpose of this discussion is to crystallize the causative factors of surgical disappointments rather than to submit statistics on personal operative successes, which will be reviewed in a subsequent communication.

CYSTITIS

Immediate postoperative cystitis is but little more frequent after interposition of the uterus than after other pelvic operations which necessitate manipulations of the bladder. It can be minimized by the avoidance of trauma, intravesical instillations of protargol after each postoperative catheterization, and the routine use of hexamethylenamine. On the other hand, a number of patients complain of the onset of bladder annoyances long after their discharge from the hospital, and are found to be suffering from chronic trigonitis. Usually several months elapse before the urinary frequency and dysuria appear and the patient seeks relief. Cystoscopic examination discloses an elevation and marked congestion of the vesical trigonum, with small additional depressions on either side, suggesting that the operator neglected to mobilize the bladder sufficiently laterally before pulling the uterus forward

(Fig. 1). This eventuates in putting the trigonum on the stretch on the posterior surface of the anteverted uterus and initiates a local circulatory stasis. The delay in the manifestation of the symptoms may be due to the fact that bacterial infection does not occur early. Culture of the urine after the patient presents herself usually reveals colon bacilli, although the *Staphylococcus aureus* is sometimes the offender. I have found the most useful therapeutic agents in the treatment of the patient's symptoms to be 7.5 gr. doses each of hexa-

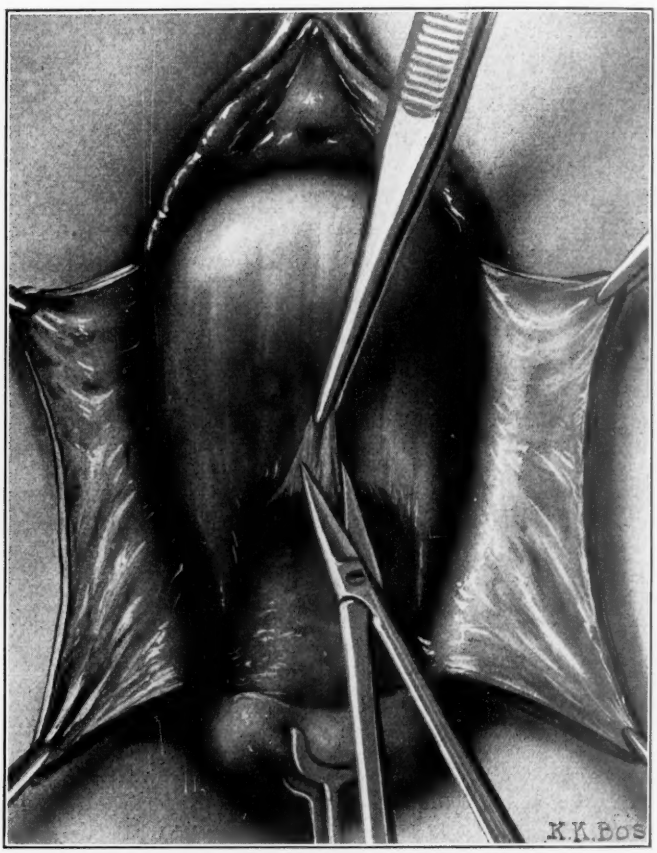

Fig. 1.—The operator has pushed the bladder well off the cervix in the midline, but has neglected to mobilize it laterally, before opening the uterovesical peritoneal fold.

methylenamin and sodium benzoate every four hours, with intravesical instillations of a 20 per cent solution of oil of cajeput in sterile olive oil three times a week. Several weeks usually elapse before the patient is comfortable without treatment. Preoperative and postoperative cystoscopic examinations are always desirable. Delayed cystitis can be avoided in most instances if the bladder is freely mobilized laterally during the dissection which detaches it from the cervix.

VESICAL CALCULI

Three patients have presented themselves complaining of marked diurnal and nocturnal frequency, severe tenesmus, and agonizing suprapubic discomfort. One had calculi in each of two lateral depressions,

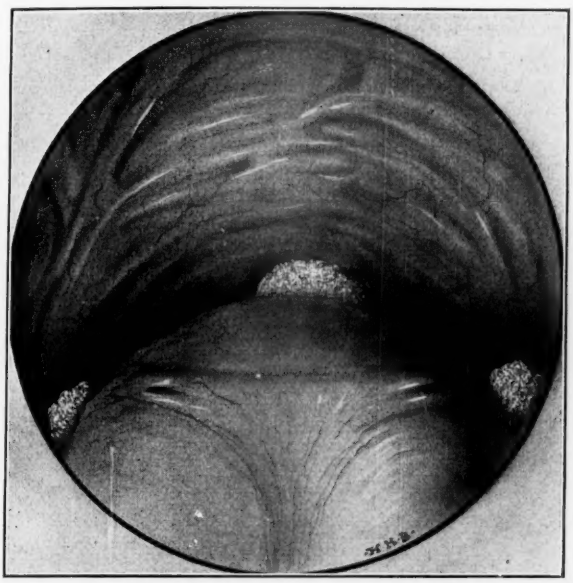

Fig. 2.—Calculi in each lateral depression and the posterior pocket.

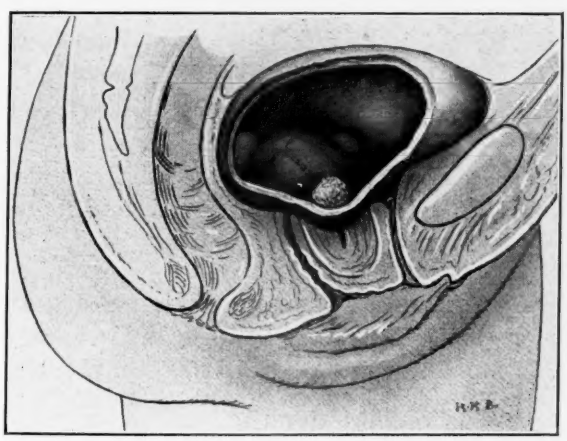

Fig. 3.—Lateral aspect of the bladder floor stretched over the underlying uterus (bladder greatly distended).

another had a stone in a large posterior pocket in the bladder behind the underlying corpus, and the third had multiple concretions in both lateral and posterior areas (Fig. 2). The urine was extremely turbid and loaded with colon bacilli in all three cases. The operations had been performed from six to 18 months before these women came under

observation. Evidently the operators had not only failed to mobilize the bladder sufficiently laterally, but two of them had also sutured the cut edge of the uterovesical fold of peritoneum too far back on the posterior surface of the cervicocorporeal junction. The latter error fixes the floor of the bladder at a level below that of the trigonum, thereby creating a posterior pocket which tends to harbor residual urine (Fig. 3). The urinary stagnation, plus the incidental passive congestion resulting from the stretching of the bladder floor, invite early bacterial infection, crystallization, and calculus formation. When the cut peritoneal margin is sutured to the surface of the posterior aspect of the extremely anteposed uterus, it should be stitched only so far back as it can be without causing tension on the bladder floor.

URINARY INCONTINENCE

Incontinence may be a symptom before operation and cured by it; or the lack of control may persist after the interposition. The relief of this preoperative disturbance can be almost assured by preceding the major steps of the operation with a Kelly plication of the vesical sphincter, although the freeing of scar tissue in the region of the urethrocervical junction and the interposition alone may suffice in an occasional case of uterine prolapse without much cystocele. It is wise to introduce two infolding mattress sutures at the bladder neck in all cases in which incontinence is a symptom. I have seen one neurotic patient who complained of a gradual loss of control several years after an interposition operation. In this instance, the annoyance may have been just another expression of the underlying neurosis.

PREGNANCY

In 1919 a multiparous patient in the childbearing age was subjected to an interposition operation by a surgeon who carefully sterilized her by tubal resection. Three months later I was confronted with a uterus nearly four months pregnant. The only way in which this paradoxical situation could be explained was that a curettage had not been done before the interposition and the impregnation had antedated the operation. Anticipating a possible rupture of the uterus before term due to an asymmetrical development and distortion of the corpus, I made the mistake of evacuating the uterus with a placenta forceps and curette through the cervical canal. Although the therapeutic abortion was accomplished, it was a difficult procedure. In two other cases of pregnancy in a transposed uterus, the gestation sac and decidua were easily removed by vaginal hysterotomy, after splitting the anterior vaginal wall (Fig. 4). I have not had the fortitude to assume the responsibility for carrying a patient to term after an interposition operation, and believe that menstrual life is a distinct contraindication for its selection. However, many gynecologists do utilize the operation in women who have not reached the climacterium, and rely with confidence upon tubal resection to prevent pregnancy. Under such circumstances the

endometrial cavity should always be curetted prior to the interposition to remove a possible attached fertilized ovum. Carl H. Ill[1] reported two cases of full-term pregnancy in young multiparas after the interposition operation with careful tubal sterilization by double ligation with linen thread, cauterization, and burial of the stumps. The first patient was in labor four days and was delivered with forceps; the second had a classical cesarean section. In the discussion of Ill's paper at the meeting of the New York Obstetrical Society, a number of similar cases were described, with complications presenting various difficulties. Hurd confessed to having omitted a curettage on one occasion, delivering the

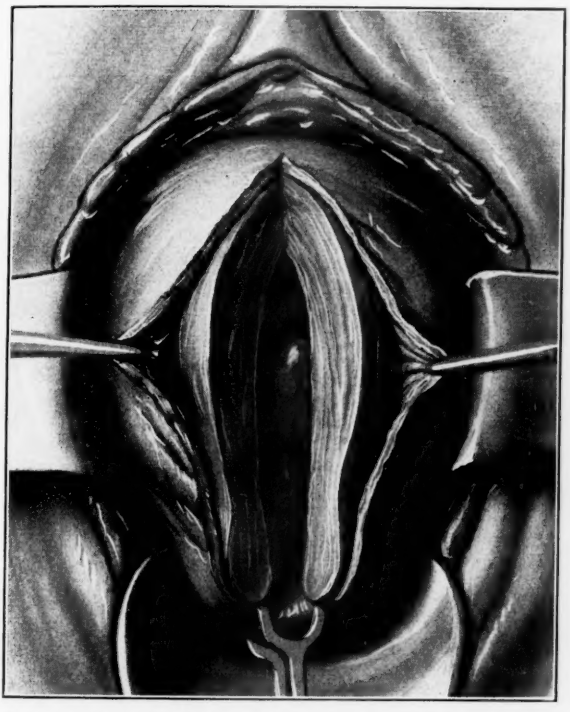

Fig. 4.—Vaginal hysterotomy, illustrating ease of evacuation of early gestation sac.

patient at term nine months later. Watson stated that he regarded interposition of the uterus as a "bad operation." A series of therapeutic problems following interposition, such as those presented during the discussion of Ill's paper, should help to establish menstrual life as an absolute contraindication. Pregnancy is a highly undesirable sequel; first, because labor is likely to be complicated, and second, because the dynamics of parturition may undo the operation.

RECURRENCE OF PROLAPSE

Several cases of "recurrence" have come under observation, one as early as ten months and another as late as seven years after operation. There are three varieties of postoperative vaginal protrusion. First,

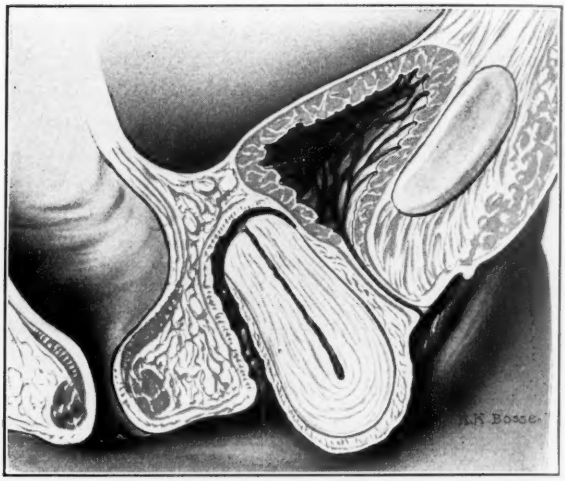

Fig. 5.—Reverse prolapse of the uterine corpus due to failure to suture the cornu to the subpubic structures.

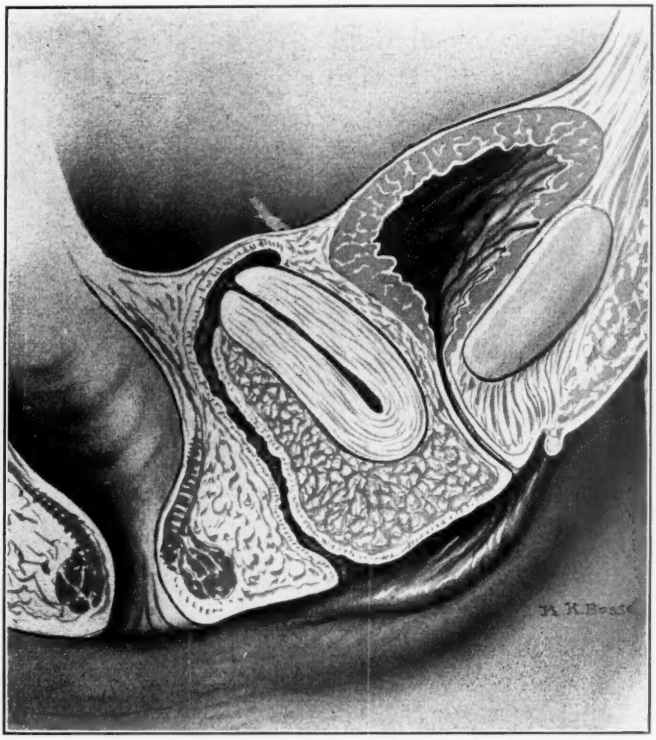

Fig. 6.—Redundancy of anterior vaginal wall, causing vaginal bulging, due to insufficient trimming of mucous membrane flaps.

that in which there is more of a reverse prolapse with bulging of the vaginal wall covering the overlying fundus than a return of a procidentia. The descent of the corpus is exaggerated when the patient strains, and it seems to be trying to dive "head-first" out of the vagina (Fig. 5). This can be ascribed to the fact that, although the uterus and vaginal wall flaps were correctly coapted and sutured, the fundus was not firmly fixed by stitching the cornu on each side to the periosteum

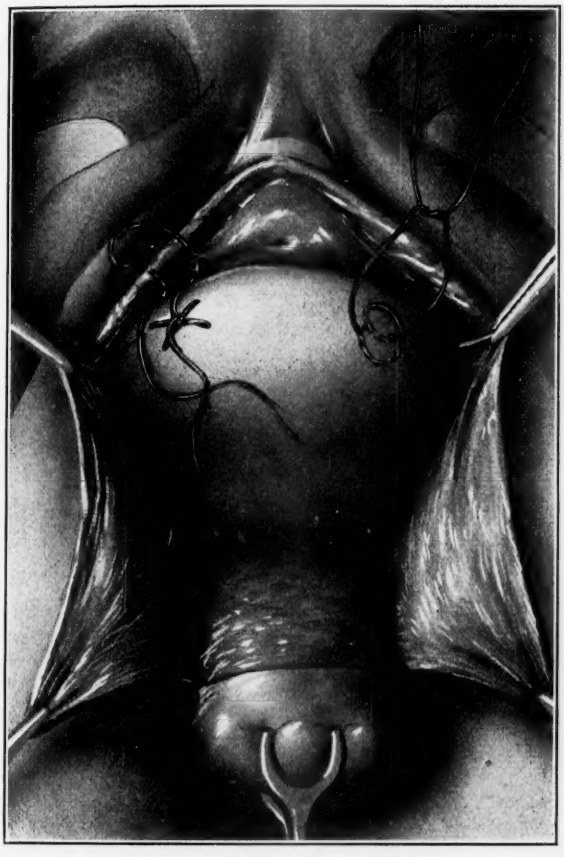

Fig. 7.—Fixation sutures of Pagenstecher linen, placed in the cornu on each side, and sutured to the firm tissues under the pubic arch.

under the pubic arch. Second, that in which there is really a recurrence of the prolapse, the uterus breaking away from the vaginal wall as a result of defective suturing or neglect to shorten the uterosacral ligaments when a high rectocele is present. And third, an apparent postoperative bulging of the vaginal mucosa when insufficient tissue has been resected laterally in trimming the flaps (Fig. 6). All of these defects are a source of discomfort to the patient, and create the impression of an operative failure.

In reoperating on these women, it is surprisingly easy to mobilize the structures concerned in the original procedure and re-do the operation. All of these embarrassing end-results can be avoided by (1) suturing the uterine cornu on each side to the subpubic periosteum with Pagenstecher linen (Fig. 7); (2) placing four interrupted master chromic sutures on the surface of the uterus, being careful to insert the lowest exactly at the junction of the corpus and cervix, as advocated by Phaneuf,[2] to obliterate the angle at the isthmus and throw the cervix

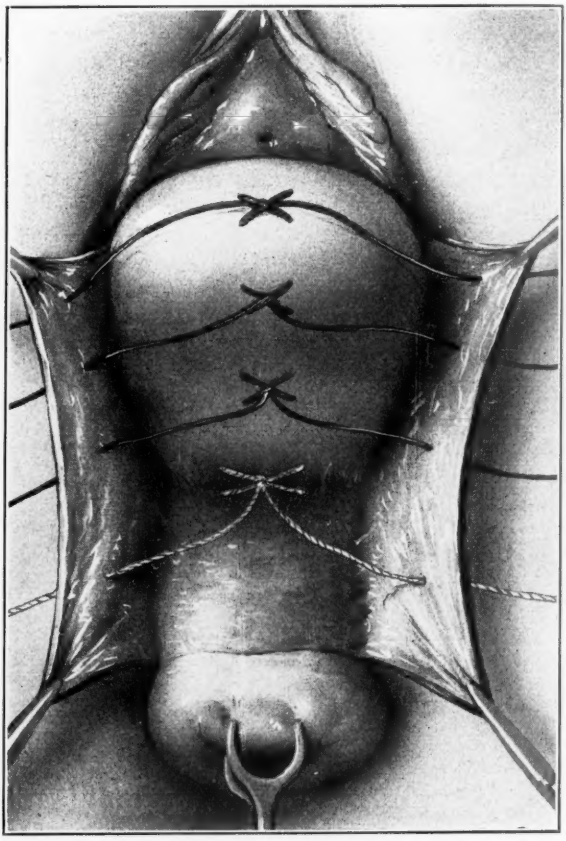

Fig. 8.—The lowest of the four master interrupted sutures (accentuated in the illustration) should be placed exactly at the cervicocorporeal junction, as advocated by Phaneuf, to obliterate the angle at the isthmus. (This step is shown before amputation of the cervix.)

well back (Fig. 8); (3) exact trimming and approximation of the vaginal flaps over the uterine corpus, without tension on the one hand, or redundancy on the other; and (4) adequate plastic repair of the perineum and posterior vaginal wall with high fixation of the rectum. When the uterus is so extremely atrophied that it is inadequate to support the heavier bladder, the Mayo vaginal hysterectomy is obviously better insurance against recurrence than interposition of the uterus.

One of the most common causes of postoperative vaginal bulging is the neglect of a posterior vaginal hernia. When an enterocele is associated with a prolapse, it must be corrected simultaneously, by free mobilization of the sac, reduction of its contents, resection, and high fixation.

FIBROMYOMA

Three patients who had been subjected to interposition operations sought relief from severe menorrhagia due to fibromyomatous tumors, two, five, and eight years, respectively, after operation. One patient was thirty-nine and the other two were forty-four years of age. In the first, the tumor was a soft myoma as large as a two months' pregnancy, and responded satisfactorily to 1,500 mg. hours of radium therapy. In the second, there were multiple hard nodules and the uterus was immobilized. They were removed by abdominal hysterectomy, which was difficult to perform without jeopardizing the bladder and ureters. In the other, the multilobular tumor mass was as large as a six months' pregnancy. Hysterectomy was regarded as unduly hazardous, radium therapy was contraindicated and would probably have proved useless, and roentgen ray therapy was employed. Hemorrhage was arrested, but the patient still suffers from a sensation of weight in the pelvis and urinary frequency. Cystoscopy shows marked extravesical pressure. It is possible that the tumors were present in each of these patients at the time of the operation and were overlooked by the surgeon. Nevertheless, such cases are a further argument against the use of the interposition operation in women who have not reached the menopause. The development of new fibroid tumors is certainly uncommon after menstruation ceases, whereas the activation and enlargement of small intramural nodules is not unusual at any time before then. When fibroids are present, or suspected because of a large uterus, or there is profuse or irregular bleeding, hysterectomy is always preferable to interposition.

CARCINOMA

One case of carcinoma of the corpus was subjected to a panhysterectomy without any particular technical difficulties. An early fundal carcinoma coexistent with the prolapse can be excluded or detected by a preliminary curettage. No instance of carcinoma of the cervix has been encountered, probably because the cervix is customarily amputated at the time of the interposition. A bleeding prolapsed uterus after the menopause should invariably be removed.

CONCLUSIONS

1. Interposition of the uterus will cure ptosis of the pelvic viscera in carefully selected cases.

2. Delayed sequelae, recurrence of prolapse, and untoward end-results can be prevented by proper attention to technical details.

3. The interposition operation should be discarded as an elective procedure in all women before the menopause.

4. The bladder should be manipulated with the utmost gentleness during the operation, but must be freely mobilized laterally.

5. Lateral and posterior pockets in the bladder floor predispose to calculus formation. The uterovesical peritoneal edge should not be sutured too far back on the posterior surface of the anteverted uterus.

6. A Kelly plication of the urethrovesical junction should be done on all patients who complain of urinary incontinence.

7. If the interposition operation is performed during menstrual life, the patient should be sterilized by tubal resection. All patients should be curetted to remove an existing fertilized ovum or to detect an early fundal carcinoma.

8. Recurrence of prolapse can be prevented by suturing the uterine cornu on each side to the subpubic structures, straightening out the angulation at the cervicocorporeal isthmus, accurate trimming of the vaginal flaps, and adequate plastic repair of perineal lacerations, rectoceles, and posterior vaginal hernias. Recurrence can be corrected by re-doing the operation.

9. A subsequent fibromyoma or carcinoma of the uterus is more likely to develop in a uterus transposed before the menopause than after it.

10. A postmenopausal bleeding uterus should be removed rather than transposed.

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DISCUSSION

DR. JOSEPH L. BAER, Chicago, Ill.—A few years ago I reported to this Society a series of 220 patients with prolapse, treated by 11 different operative procedures. Among those procedures the interposition operation held the leading place, being used in 40 per cent, or 91 patients. For a great many years the gynecologic staff at the Michael Reese Hospital had favored this operation, hence the dominant position that it held. At the beginning of 1929 we began to interest ourselves in other methods of procedure, and the interposition operation has now a frequency of something less than 10 per cent instead of 40 per cent.

I am in accord with each of the points made by the essayist with perhaps the exception of the contraindication to the use of the interposition operation in women during menstrual life. Operative sterilization was done in 49 of our series and there was one postoperative x-ray sterilization. We had just one subsequent pregnancy. That patient was allowed to go to term and at term was treated by a section and sterilization. I am not as much afraid of a subsequent pregnancy as is the essayist because one of two things happens: either the patient aborts spontaneously, or the uterus is emptied by the operator in early pregnancy or at term.

Our immediate postoperative results in that series of 90 were as follows: 1 death occurred from embolism; 38 patients had a temperature of 101° for one or more

days; 10 had 101° or more for seven days. The complications included an infected perineum in two instances, an infection of the perineal wall which persisted for several days, pelvic abscess in two instances, and sepsis and shock in one patient with satisfactory cure.

In connection with treatment of the bladder, the man who originally devised this operation emphasized freeing the lateral attachments, as described by Dr. Dannreuther. Failure to do so has resulted in "horseshoe bladder" and not infrequently there has been calculus formation. Spalding advocated dividing the ligaments on each side in order to meet specifically that problem in the operation. Catheterization was not required in over one-half of our series, 57 per cent. There was very little postoperative cystitis.

The hospital stay averaged seventeen days. In follow-up examinations there was a satisfactory result in 92 per cent of those whom we were able to reach, which is a very high percentage of satisfaction with this operation. The important preoperative symptoms had been protrusion, backache, and urinary frequency.

I do not favor Pagenstecher linen for fixing the cornua to the periosteum, but prefer kangaroo or forty-day chromic catgut. It is important that the fundus be anchored just back of and under the symphysis, for if it is in front of the symphysis or merely under it the fundus may protrude. It is vital that the cervix be amputated if the uterus is more than 8 cm. in length.

In replacing the interposition operation in these last eight years, we have added two others to our repertoire. One is the vesicofixation operation of Halban-Porges, which is excellent but not so good for the large cystocele type but which gives excellent fixation and has the advantages of the interposition operation. The second is the modified Fothergill with which we are becoming more and more pleased as the years go by. I think it may some day take first place for cure of prolapse of the uterus. Neither of these operations requires sterilization.

DR. RICHARD W. TELINDE, BALTIMORE, MD.—There is a procedure employed in the Johns Hopkins Clinic postoperatively which I do not believe is in very general use. Some years ago one of our men when visiting Dr. John Clark's clinic found that they gave a liter of fluid by bowel while the patient was still in the operating room. I believe they used 5 per cent sodium bicarbonate solution with two or three ounces of mineral oil in the liter. This procedure assures a good quantity of fluid during the first postoperative hours.

We combine this with an instillation of 1 per cent mercurochrome into the bladder, not for any bactericidal effect, but because of its irritative properties. The bladder irritation gives rise to a desire to void as soon as the patient awakens from her anesthetic, and she often calls for the bed pan before she is fully conscious. She starts to void small amounts, 25, 50, 100 c.c., and within six or eight hours she is usually voiding 200 c.c. or more. We carry out this procedure as a routine in major gynecologic operations, including the interposition operation. Craig reported a series from our clinic some years ago and the incidence of one or more postoperative catheterizations was reduced 60 per cent to 7.7 per cent. If the output is 200 c.c. or more very few of the patients will be found to have residual urine.

IMMEDIATE REPAIR OF CERVICAL INJURIES

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(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

MANY obstetricians and obstetric authors have taken a very conservative position concerning cervical injuries. Their attitude has been that routine inspection of the cervix is not advisable and immediate repair of cervical injuries should only be done when necessary for the control of bleeding. Some years ago I published the results of a series of cases in which immediate repair had been done, and since that time, we have continued to inspect the cervix after labor and to repair it at once if it appeared necessary. That the conservative stand of former years is beginning to be replaced by a more active one is evidenced by the appearance of papers by DeLee, E. P. Davis, Skeel, Bubis, Emge and, more recently, Goff and George Gray Ward. Goodall, in his monograph on puerperal infection published in 1932, expresses himself quite clearly when he says "it is my firm conviction that within five years it will be considered as bad practice in hospitals to leave a cervical tear unrepaired as it would be considered culpable today to leave a perineal tear unsewn."

There have been two arguments against immediate suture: first, that sutures put in while the cervix was soft and succulent, as it is immediately after labor, would not hold, and second, that infection might follow. An experience extending over a considerable number of years has convinced us that, with careful technic, satisfactory results are obtained in about three-fourths of the cases. We are also quite convinced that the fear of infection is greater than it need be. We have not been able to note any increase of morbidity which could be traced to cervical suture.

The importance of cervical lesions is sufficiently great that it appears warranted to inquire what may be done to decrease their extent. A very large part of cervical abnormalities are in whole or in part a result of the trauma of parturition. This is, in considerable part, unavoidable. The cervix of every woman who delivers a child is injured to some degree. In many cases the injury is so slight that a return to the condition which existed prior to labor is almost attained. In others the stretching or partial laceration of the tissues of the side of the cervix produces more or less ectropion after involution is complete. With the purpose of determining the character of labor which is most prone to produce injury to the cervix and the forms of interference which are most often followed by cervical damage, I have made a study of the

cervical injuries which have occurred in a series of cases in our service, noting the relationship of cervical injury to parity and to various forms of operative intervention. Routine examinations are made rectally, vaginal examinations being used only when the information obtained by rectal examination is insufficient. Chemical sterilization of the vagina is not employed.

I have gone over the delivery records of 3,534 patients, in which study I wish to acknowledge the assistance of Dr. R. M. Grier, in order to ascertain the type of labor in which lacerations of the cervix are most frequent. We also desired to ascertain the forms of delivery most likely to cause cervical injury. We have for a number of years made very liberal use of the outlet forceps operation. It has not seemed to us that this procedure could cause cervical trauma, as, at the time the forceps delivery is done, the head has already escaped from the cervix. Other operative procedures are far more likely to injure the cervix.

This series of cases contains 1,596 primiparas and 1,938 multiparas. It has been our custom for years to examine the cervix in all primiparas and in all multiparas, except those who have had a very easy spontaneous delivery. In all others the cervix has been exposed with specula and its entire circumference carefully inspected. All tears greater than 3 cm. in length are sutured. Small lacerations are let alone. After involution has taken place there usually appears only a small indentation, and in some cases the injury is no longer noticeable. In some cervices, in which notable lesions occurred during labor, a later ectropion may be found.

TABLE I

Total number 3,534	
Primiparas	1,596—11.2%
Multiparas	1,938— 4.1%
Both	— 6.3%

The routine inspection of the cervix consumes but little time and the additional manipulation has not increased morbidity. Adequate exposure must be obtained by a broad retractor upon the perineum. A narrower lateral retractor is, in most cases, also needed. The necessary exposure of the cervix should be done with light ring forceps of the type suggested by DeLee. Volsella should not be employed as they add to the wounds already caused by the labor and are likely to tear the soft, succulent cervix. Goff has drawn attention to an important point in the visualization of cervical injuries. If the ring forceps grasps the anterior and posterior lips at the middle point, the softness of the puerperal cervix permits it to stretch and to be drawn out to such a degree that a laceration at one side is difficult to recognize. The ring forceps should grasp the cervix at points roughly corresponding to 2 and 4 and 8 and 10 on the clock dial. Only gentle traction must be used, merely enough to steady the cervix and hold it in position for inspection and suture. I have included in this series only those lacerations which seemed to re-

quire attention, that is, those of 3 cm. or more in length. Small injuries heal well. It is often stated that large ones do. If this is so, the origin of the deep lateral defects found in many cervices is difficult to explain. In primiparas injuries of this extent were found in 11.2 per cent, in multiparas in 4.1 per cent, an average for the entire series of 6.3 per cent.

If primiparas are considered alone, we find a definite variation in the incidence of injury in the cases of anterior vertex presentation as compared with posterior vertex or breech. These figures are shown in Table II.

TABLE II. PRIMIPARAS

L.O.A.	711	63 tears— 8.8%
O.D.A.	403	29 tears— 7.2%
O.D.P.	254	41 tears—16.1%
L.O.P.	166	34 tears— 8.0%
Breech	63	12 tears—19.0%
Others	7	1 tear — 6.0%

The number of right anterior positions in this report seems to me to be too great. This is probably due to the fact that some cases were recorded by the interne as anterior which were posterior earlier in labor. Dilatation is slower in posterior positions, and the operative interference often needed to terminate the labor may influence the number of lacerations. Cervical lacerations in breech deliveries in primiparas are notably increased, there being injury which required surgical attention according to the standard given above in 19 per cent.

TABLE III. MULTIPARAS

L.O.A.	969	42 tears—4.3%
O.D.A.	551	24 tears—4.3%
O.D.P.	197	11 tears—5.5%
O.L.P.	130	9 tears—6.9%
Breech	79	1 tear —1.2%
Others	6	0 tears—0

In multiparas the difference in frequency in anterior and posterior positions is much less marked, but the frequency of injury is somewhat greater in the posterior position. In Table IV, in which primiparas and multiparas are assembled, a marked difference in incidence of injury appears, the number being definitely greater in posterior occiput and in breech positions.

TABLE IV. PRIMIPARAS AND MULTIPARAS

L.O.A.	1,680	105 tears— 6.9%
O.D.A.	954	53 tears— 6.5%
O.D.P.	451	52 tears—11.0%
L.O.P.	296	43 tears—11.1%
Breech	142	13 tears— 9.1%
Others	13	1 tear — 7.6%

Spontaneous delivery occurred in 1,470 patients, of which 264 were primiparas. Of the primiparas 36, or 13.6 per cent, sustained lacera-

tions which needed attention. In the multiparous deliveries, 1,206 in number, only 4.1 per cent received injury. It seems worthy of emphasis that notable cervical injury may occur a little less often than once in seven cases.

TABLE V. SPONTANEOUS DELIVERY

Primiparas	264	36 tears—13.6%
Multiparas	1,206	50 tears— 4.1%
Both	1,470	86 tears— 5.1%

In the primiparas delivered operatively, there is a widely varying incidence of injury as is shown in Table VI. It is interesting to note that

TABLE VI. TYPES OF OPERATIVE DELIVERY. PRIMIPARAS

Low forceps	1,090	105 tears— 9.6%
Midforceps	77	22 tears—28.6%
High forceps	1	0 tears— 0.0%
Version—forceps on after-coming head	13	3 tears—23.3%
Version—no forceps	9	2 tears—22.2%
Breech extraction with forceps	28	8 tears—28.5%
Breech extraction—no forceps	33	3 tears— 9.0%

in the cases terminated by outlet forceps delivery, laceration was found in 9.6 per cent, while the primiparas who delivered normally had tears in 11.2 per cent. I believe that the explanation for this difference lies in the fact that, as we are accustomed to use outlet forceps very freely, only those primiparas deliver spontaneously who are progressing rapidly. The frequent use of forceps, especially in primiparas, when the head is upon the perineum, if skillfully done, is a conservative rather than a radical procedure. Injury to the cervix in these cases occurs nearly always, if not invariably, during the last third of the process of dilatation. We have many times found injured cervices in cases in which the last part of the first stage had progressed rapidly, when we were quite certain that no laceration existed earlier. The incidence of injury was not influenced by the forceps operation. We have observed that in primiparas, whose cervices dilated rapidly, lacerations were found after delivery in a number of cases. It seems that a very rapid first labor is not invariably an unmixed blessing. A thickened edematous cervix may increase the difficulty with which lacerations are seen. This condition is found in women whose labors have been long. Cases of posterior position in which the anterior lip has been traumatized between the head and the symphysis may produce this condition. Submucous hemorrhage is seen resembling the color about a black eye. After a normal labor the cervix is not greatly thickened.

Experience in a number of clinics appears to indicate that outlet forceps deliveries skillfully done do not subject either the mother or the child to increased risk. The cervix participates in this immunity to increased injury. This would seem inevitable, as, when an outlet de-

livery is done, the head has already escaped from the cervix. In multiparas the incidence of injury is less than 1 per cent greater in outlet forceps deliveries than in spontaneous births. Midforceps, however, shows a great increase in cervical injury, 28.6 per cent in primiparas

TABLE VII. TYPES OF OPERATIVE DELIVERY. MULTIPARAS

Low forceps	532	26 tears— 4.8%
Midforceps	26	3 tears—11.5%
High forceps	1	0 tears— 0.0%
Version plus forceps	18	1 tear — 5.5%
Version—no forceps	20	0 tears— 0.0%
Breech extraction—plus forceps	19	1 tear — 5.2%
Breech extraction—no forceps	44	0 tears— 0.0%

and 11.5 per cent in multiparas. Many of these cervices dilated slowly, and among them are a considerable number of cases of posterior position which required some form of interference. Midforceps deliveries are not done until it appears that complete descent will not take place or, at least, will not occur within a safe length of time. An active second stage is not permitted to continue more than two hours unless definite progress is being made. An unduly prolonged second stage exposes the woman to the possible danger of a retraction ring. In comparing the number of tears in primiparas delivered by version and extraction and those in whom the breech position was present primarily, we find that breech extraction without preceding version and with forceps on the after-coming head shows a higher incidence of injury than version and extraction or extraction without forceps. All patients with breech presentations are delivered, if possible, by the Mauriceau maneuver, forceps being used if any difficulty is encountered and if more than a very moderate force is needed. This causes the forceps to be employed chiefly in the cases in which the head does not easily slip through the cervix. In these cases the Piper forceps are very useful. Intervention before dilatation is complete in breech presentation is a serious error.

A consideration of the results of this series indicates that properly done outlet forceps deliveries do not increase the incidence of cervical injury. The number of injuries which require surgical attention according to the standard already given is probably greater than many obstetricians believe.

For the management of cervical lacerations various plans have been proposed. It has seemed to us that immediate repair is preferable to

TABLE VIII. TYPES OF OPERATIVE DELIVERY. PRIMIPARAS AND MULTIPARAS

Low forceps	1,622	131 tears— 8.0%
Midforceps	103	25 tears—24.2%
High forceps	1	0 tears— 0.0
Version—plus forceps	31	4 tears—12.9%
Version—no forceps	29	2 tears— 6.8%
Breech extraction—plus forceps	47	9 tears—19.1%
Breech extraction—no forceps	77	3 tears— 3.9%

suture done later during the puerperium, on the fifth or the tenth day. It is true that immediately after labor the cervix is soft, but due attention to technic is followed by results sufficiently satisfactory to make the plan worth while. It is true that in some instances a notch in the cervix may indicate the location of the tear at the end of the puerperium. If the major portion of a deep injury may be made to heal, the resulting ectropion is reduced or prevented.

In order to obtain healing which is satisfactory a rather definite plan must be followed, the essential points of which will be indicated. DeLee, some years ago, pointed out, and we have confirmed his observation by the examination of many lacerated cervices, that the muscular structure of the injured cervix retracts, so that the cross-section of the torn edge of the cervix forms a "V," the two arms of the "V" being the mucosa of the cervical canal and the vaginal surface of the cervix, respectively. The sutures then must go sufficiently deep to grasp the retracted muscle. If the suture passes only through the arms of the "V," or the edges of the mucosa, it will inevitably cut through. The operator must sacrifice to a certain extent the desire to make an extremely neat suture line and place the suture deeply enough to grasp the muscular portion of the cervix. As the tissues grasped by the suture are very soft, they must be tied with but little force. In the presence of an abundant blood supply, healing is rapid. Suture material of long life is, therefore, not needed. Care must be exercised during the placing of sutures that too much traction is not put upon the cervical lips in the desire to obtain good exposure. It is easy to stretch them or to elongate one more than the other, thus causing an uneven approximation.

It has been logically urged by a number of writers that an attempt should be made after labor to restore the cervix to as nearly normal a condition as possible. It seems even more reasonable that the obstetrician should endeavor to decrease the need for restoration. Primary cervical repair is a procedure for the hospital and for the obstetrician. The physician who is not trained in vaginal plastic work should pursue the older and more conservative course of suturing only those cervices which bleed sufficiently that hemorrhage must be controlled.

Our experience would indicate that the employment of the more serious forms of interference should be as limited as possible. Outlet forceps delivery does not increase the incidence of cervical injury. Bags should be used as infrequently as possible and manual dilatation, or Dührssen's incisions should be employed only upon the clearest indication. In the management of the lacerations which occur in spite of this conservative treatment, primary repair appears definitely to lessen later cervical abnormality.

DISCUSSION

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—Dr. Danforth's paper admits of little discussion because of the accuracy and soundness of his conclusions. I may therefore say with great brevity that lacerations occur with great frequency

even in vertex presentation; second, that we should not minimize the effect of the delivery of the shoulders in adding to the laceration of the cervix; third, that to our considerable surprise in the observation of a large number of patients treated by the so-called Slemmons' method of induction, our incidence of laceration was considerably reduced; fourth, that lacerations of the cervix, as of the perineum or of the anterior vaginal wall, are wounds requiring suture; fifth, that the discovery of cervical lacerations may in most instances be made with simple digital examination without exposure.

Last, repair of the cervix is productive of no increase in morbidity so far as our figures tell us, and is a procedure of great simplicity. The only point which we have found of value has been in a considerable number of cases of deep unilateral laceration to apply the lowermost suture first, carefully coapting the lips of the wound, climbing up the tear, as it were, rather than beginning at the apex.

DR. ROBERT L. DICKINSON, NEW YORK, N. Y.—I would like to say that this is one subject which we can perhaps best teach with pictures. Moreover, I speak for three-dimensional representations, and some day we are going to have adequate museums of models. My students were taught to repair, not on the living being, but by flexible molds of the severely lacerated pelvic floor and cervix. That is one of the ideas that I have never sold to the medical public but it is bound to come because you can only learn by doing. Having written two papers on this subject many years ago, I can speak with feeling. The first advocated immediate repair. The second reported the experiment of waiting for two or three days. There is an enormous edema and distortion immediately after delivery, the size of the anterior lip making it difficult to recognize the anatomy. This is also true of the pelvic floor injuries. Waiting until the edema had subsided, I could recognize anatomy that could not be recognized before.

DR. EARDLEY HOLLAND, LONDON, ENGLAND.—At home we are very conservative in this respect. Yet it seemed to me that, although the essayist had presented what I should call a radical measure, it was presented by a very conservative man.

Consideration of this matter leads at once to the question, of which is better domestic midwifery or hospital midwifery? There is not the slightest doubt that in a few years' time nearly every woman will have her baby in a properly equipped maternity hospital, and then we shall be able to do these things with impunity. But it would be dangerous to teach the students or the general practitioners that they should do prolonged repairs of the cervix, because if they did I am sure it would be disastrous. Yet I feel convinced that in our hospital work we should do repairs and that it will have a most astonishing effect in gynecologic practice. I suppose that the most common pathology we meet with in our practice is that of the cervix. When Dr. Danforth examines the patients in whom he has repaired the cervix, does he find what I would designate as a bell-shaped cervical canal? A very important point of technic must be the inclusion of all the retractor muscles in order to avoid finishing the repair later.

DR. DANFORTH (closing).—This operation is a specialist's procedure and not one which we teach to men who are going into general practice.

I believe I stated that we did not have 100 per cent perfect results. I do not think one can expect that, in dealing with a soft puerperal cervix, but the results are sufficiently good, so that we have been encouraged to continue.

One should be careful to get all of the muscular layers and this requires a suture which goes rather deeply. One must forego the desire to make an artistic suture line and place the sutures in what may appear to be rather a coarse manner. Plain catgut is preferable to chromic as healing is rapid.

RELATIONSHIP OF ACANTHOSIS NIGRICANS TO ABDOMINAL MALIGNANCY*

Report of Cases, Including One in Which the Primary Growth Was in the Pelvis

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ACANTHOSIS NIGRICANS is a condition well recognized by dermatologists, and the microscopic picture of the cutaneous lesions is diagnostic. We are satisfied, however, that the condition and its significance are not well understood by clinicians and surgeons, especially as regards the adult types of the disease which are associated in the majority of cases with malignancy in the abdomen.

Acanthosis nigricans was first described by a dermatologist, Pollitzer, in 1890, and also independently in the same year by Janovsky. In 1909 Pollitzer reported a total of 53 cases in the literature, in 5 of which cancer of the uterus was present with extension to the sympathetic nervous system. Since attention has been called to the condition, many papers on the subject have been written, and about 250 cases have been reported. It is probable, however, that in many cases the condition is not diagnosed or at least is not reported. Pollitzer, in a discussion of Knowles's paper on the subject, said that 4 cases were not reported for every one that was.

Acanthosis nigricans may be divided into the juvenile and adult types. In the juvenile type, there are many supposed etiologic factors,[2, 12] for example, those with a direct or indirect effect on the chromaffin and sympathetic systems, including metabolic disturbances; various toxins; achlorhydria; endocrine diseases, such as involvement of the thyroid gland, pituitary body, testes,[4] ovaries, suprarenal glands, pancreas and thymus; inflammatory and traumatic conditions affecting the stomach and chromaffin system; congenital anomalies and hereditary factors, and tuberculosis. Even syphilis and the effect of sunlight on the enzymes in the skin have been incriminated. Actually the etiology of either the juvenile or adult forms of acanthosis nigricans remains to be proved. The juvenile type runs a benign course, except in rare instances such as in cases of perforation of a duodenal ulcer or in those of severe diabetes. There is no associated malignant condition.

We are especially interested in the adult types of acanthosis nigricans. The same factors that predispose to the juvenile form of the disease may occasionally be encountered in older people,[1] and the unexplained frequent association of acanthosis nigricans with cancer is of special concern.

*From the Mayo Clinic.

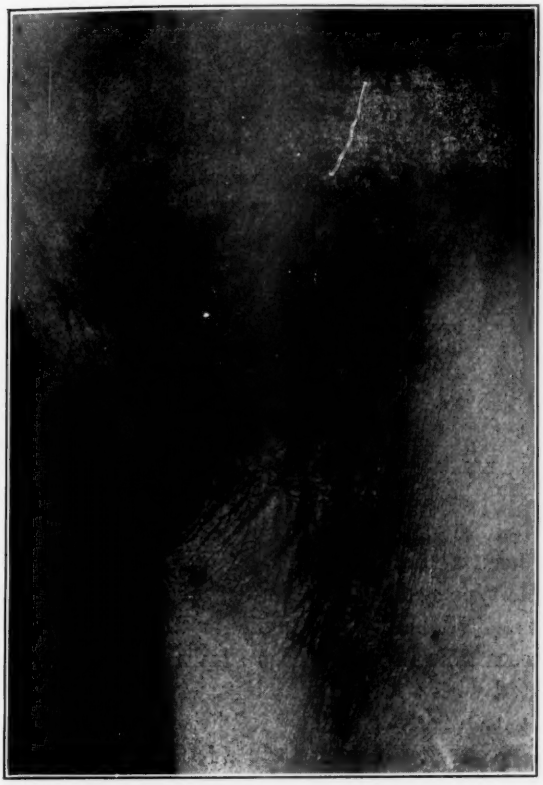
The cutaneous picture is the same in both the juvenile and adult types of acanthosis nigricans, no matter what the precipitating etiologic factor may be. The axillae, neck, external genitalia, and other flexural surfaces become pigmented, in that order. There are in addition to this pigmentation marked verrucous and papillomatous changes, hyperkeratosis and exaggeration of the normal cutaneous markings. In a third of the cases in which women are affected by the disease, the verrucous and papillomatous, and even condylomatous lesions, involve the labia and vagina. Lesions usually appear first in the axillae or on the neck, and in more than half the cases there are changes in the mucous membranes, although pigmentation is a much less frequent finding in the latter cases.

In the early stages of acanthosis nigricans very little thickening of the skin may be present, so that differentiation from Addison's disease may be difficult. While both Addison's disease and acanthosis nigricans show essentially the same distribution of pigmentation and both involve the suprarenal chromaffin and sympathetic systems either directly or indirectly, no explanation is available why in Addison's disease there is pigmentation only of the skin whereas in acanthosis nigricans, within a short period of time, there are in addition verrucous and other changes in the epidermis (Figs. 1 and 2). Hemochromatosis may be associated with increased melanin pigmentation, but again the accentuation of the markings of the skin and the verrucous changes seen in acanthosis nigricans are absent in the former condition. The latter changes are also lacking in other pigmentary dermatoses.

It is important to distinguish benign pigmentation with verrucous and papillomatous lesions which may be encountered in the axillae of women, and also extensive verruca senilis and dermatosis papulosa nigra in negroes from acanthosis nigricans.

The histopathologic picture is usually typical and, as has been said,[8] is diagnostic. It is characterized by the following features: relative and absolute hyperkeratosis (increase in the thickness of the stratum corneum); marked irregular acanthosis (proliferation and increased thickness of the prickle cell layer) with adjacent areas of atrophy of the prickle cell layer; elongated narrow papillary bodies; dense melanin pigmentation of the basal cells of the epidermis; a few chromatophores laden with pigment, which are limited chiefly to the papillary bodies, and usually absence of any amount of inflammatory reaction in the cutis.

It is interesting to note that among patients with acanthosis nigricans who are le[illegible] twenty years of age malignancy is rarely, if ever, found, on[illegible] oubtful case of malignant deciduoma of the uterus, of a patient [illegible]en years of age, having been reported.[13] Based on an analysis of Mukai's statistics for patients between twenty-one and thirty years of age, cancer may be associated with acanthosis nigricans in 23 per cent of cases, and for patients from thirty-one to forty years of



A.

B

Fig. 1.—*A*, axilla; *B*, beneath breast: Showing increase in pigmentation, thickening of skin with accentuation of normal skin markings and warty lesions.

age in 53 per cent of cases. When patients are more than forty years of age, cancer is found in 75 to 80 per cent of the cases. The probability in such cases is that the primary tumor or a metastatic growth involves or presses on some part of the chromaffin or sympathetic nervous system and the outlook is always grave. In other cases liberated toxins are probably responsible.

The relationship between disease of the suprarenal glands and acanthosis nigricans is still debated by many authors, including Grace and Schwartz and Mook and Drews. Others do not believe that the disease, at least the adult type, is in any way related to disturbances of the endocrine system. On the other hand, the fact that the majority of cases reported (according to Mukai the total number of cases reported is 117 of juvenile and 94 of adult acanthosis nigricans and seven which he could not classify) are of the juvenile type and in them the disease develops during the active growing years, gives weight to the views expressed by some authors (Knowles and others) that the disease is of endocrine origin.

We have encountered 13 cases of acanthosis nigricans at the clinic, 5 of the juvenile type and 8 of the adult type. In 5 of the latter cases, the condition developed before the patients were forty years of age. In four cases acanthosis nigricans was shown by microscopic examination to be associated with abdominal malignancy (in three cases with cancer and in one with sarcoma). The following case (Case 1) is given in some detail because it illustrates the association of acanthosis nigricans with pelvic malignancy:

ACANTHOSIS NIGRICANS ASSOCIATED WITH PELVIC MALIGNANCY

CASE 1.—The patient, a woman, first came to the clinic in 1919 when she was forty-seven years of age. She had menorrhagia which was sufficiently severe to produce mild secondary anemia. She was given 410 mg. hours of radium treatment and was markedly benefited. She passed through the menopause about a year later with little trouble. She again returned to the clinic in 1926 with definite symptoms of exophthalmic goiter, and after appropriate medical treatment and partial thyroidectomy made an excellent recovery.

In 1928, or about eight years after her menopause, the patient again returned to the clinic complaining of irregular vaginal bleeding which was first noticed as a mere spotting shortly after thyroidectomy about two years previously. A diagnosis of degenerating hypertrophic endometrium was made from a curetted specimen. She was given 1,184 mg. hours of radium treatment and all bleeding stopped.

The patient was not seen again at the clinic until September, 1935, at which time she complained of an uncomfortable, dry feeling in her mouth, poor appetite, and the loss of twenty pounds (9.0 kg.) in four months. She had also noticed that since June, 1935, the skin of the axillae, of the neck, beneath the breasts, and in other regions was becoming darker and also verrucous. She had a history of qualitative food distress, with attacks of bloating and belching which, as a rule, were relieved by taking soda or by vomiting, but which on a few occasions had required a hypodermic injection of morphine. Jaundice was never noticed. She had no complaints referable to the pelvis but, on pelvic examination, an irregular fixed

mass could be felt which was larger than when she was last examined at the clinic seven years before. There had been no uterine bleeding in the meantime. A diagnosis of acanthosis nigricans was made (Figs. 1 and 2 *a*) with probable malignancy in the abdomen, and exploratory operation was advised.

After an interval of two months, the patient again returned complaining of cramping pains in the lower part of the abdomen and of increased loss of weight. Operation was again urged and the patient consented. Dec. 4, 1935, under general anesthesia, panhysterectomy was performed for an extensive adenocarcinoma of the body of the uterus, the growth being adherent to one loop of small bowel and to the base of the bladder and having extended out into the base of the left broad liga-

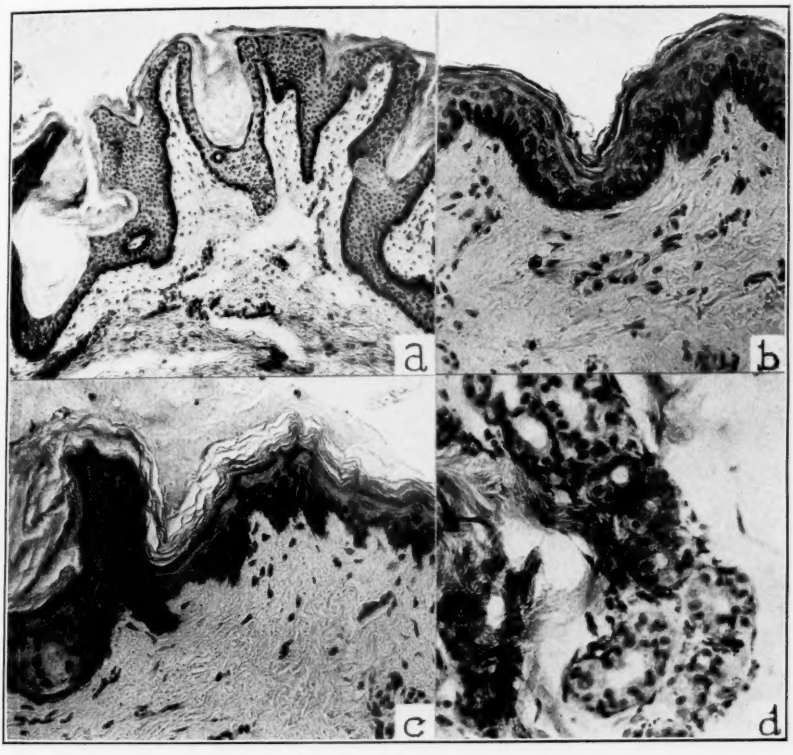


Fig. 2.—*a, Acanthosis nigricans* (typical picture); relative and absolute hyperkeratosis, keratotic plugging, irregular thickening of prickle-cell layer and increased pigmentation of basal cells of epidermis (× 80); *b, Addison's disease,* typical capping of basal cells of epidermis with melanin and numerous chromatophores in the cutis laden with pigment; no significant changes in epidermis (× 320); *c, Arsenic pigmentation,* relative and absolute hyperkeratosis, atrophy of prickle-cell layer, pyknosis and palisade arrangement of basal cells laden with melanin pigment; also, chromatophores in cutis (× 320) (all silver nitrate and hematoxylin stains); and *d,* hemochromatosis, granules of hemosiderin of varying size (staining block) deposited in propria of sweat glands (× 320 iron stain).

ment. The prospect for cure was not good because of the extent of involvement, but all visible evidences of the growth were removed. No apparent metastatic involvement of the aortic lymph nodes or liver was noted. Multiple gallstones were palpated in the gallbladder. One course of roentgen treatment was administered. This patient is, at the moment of writing (April 4, 1936) still alive and much improved; there is no indication of local recurrence or metastasis, although the pig-

mentation and verrucous changes have increased. There is a large plaque near the sacrum and involvement of the internal parts of the labia, as well as verrucous folds of the mucous membranes of the mouth but without pigmentation of the latter.

In the following seven cases of acanthosis nigricans of the adult type the condition was either definitely or presumably associated with abdominal malignancy:

ACANTHOSIS NIGRICANS ASSOCIATED WITH ABDOMINAL MALIGNANCY

CASE 2.—A man, thirty years of age, came to the clinic Dec. 28, 1921, complaining of indefinite pains in the upper portion of the abdomen and epigastrium. General physical examination gave entirely negative results, except for indicating marked pigmentation about the neck, axillae and inguinal folds, which the patient said had originated during the previous two months. He was dismissed. He returned about four months later after having continued to lose weight. The cutaneous lesions had become darker and there was definite thickening in these areas with warty-like growths. A clinical and histopathologic diagnosis of acanthosis nigricans with the possibility of malignancy in the abdomen was made. On April 14, 1922, the patient underwent an exploratory operation and multiple nodules were found in the liver. Microscopic study of these nodules revealed adenocarcinoma of Grade 1. The primary tumor could not be found. Convalescence was uneventful and the patient was dismissed April 20, 1922. We received information later that he died in August, 1922.

CASE 3.—A white man, thirty-eight years of age, came to the clinic Dec. 19, 1922, complaining of irritability of the stomach, which had been present for two years. In the fall of 1921 he had first noted the development of a brownish pigmentation on the first finger of his right hand. This had become more marked and later the skin of the entire body had become involved, pigmentation being more diffuse on all exposed areas and being particularly marked around sites of irritation, such as the waist band, calves of the legs and in the axillary and inguinal regions. The skin in these regions had become thickened and harsh. A diagnosis of acanthosis nigricans was made and confirmed histopathologically at the time of operation. At operation, December 23, an extensive carcinoma of the stomach was found and, because of obstruction, posterior gastroenterostomy was performed. The patient died about eight months later from carcinomatosis.

CASE 4.—A white woman, thirty-nine years of age, first came to the clinic July 14, 1925, because of obstruction of the common duct following cholecystectomy, which had been performed elsewhere. Gastroduodenostomy was performed because of gastric ulcer and the common duct was reconstructed over a catheter. Five years later she again returned to the clinic with jaundice. At this time there was also diffuse brownish pigmentation with thickening of the skin at points of pressure. Biopsy revealed the typical picture of acanthosis nigricans. The catheter was removed from the common duct and the patient recovered uneventfully. We learned that she died a year later, apparently from metastasis.

CASE 5.—A negro, fifty-six years of age, presented himself at the clinic Sept. 6, 1928, stating that about six months previously he had noted that the skin on his neck was becoming darker and that his hands were getting very rough. His tongue had become cracked and was thickened. The skin about his eyelids, in the axillae and groin, and about the joints had also become dark and thickened and he noticed generalized pruritus. There was a warty growth on his lower lip, and this was removed surgically. There were smaller warts on his lips, gum margins, and

face and hands. Beginning in January, 1927, he had been treated for ten weeks for gastric ulcer. The diagnosis of ulcer had been confirmed roentgenologically. Because of the close association of acanthosis nigricans (confirmed on this case by microscopic studies) and abdominal malignancy, exploration was thought advisable but the patient declined. He died Nov. 1, 1928, and postmortem examination was not made. The rapid onset of the condition and the fact that the patient died within a year and a half is strongly indicative of a malignant condition.

CASE 6.—A white man, twenty-nine years of age, came to the clinic July 16, 1929, complaining of itching in the axillary and inguinal regions of three months' duration. Verrucous lesions had then appeared and the skin had become very thick and dry. A general examination and detailed laboratory studies gave essentially negative results. A definite diagnosis of acanthosis nigricans was made. Exploratory operation was performed July 25, 1929, but with completely negative results. The patient died at home about five months after he was first seen at the clinic, the evidence on the basis of history, symptoms, and duration of the condition favoring a neoplastic process.

CASE 7.—A white woman, aged thirty-seven years, came to the clinic Feb. 22, 1932, complaining of rheumatism, dyspepsia, and menstrual irregularity. She had areas of deep pigmentation about the eyes, axillae, trunk, and genitalia. The left lobe of the liver was definitely palpable 10 cm. below the costal margin and examination of the fundus of the uterus revealed multiple uterine fibroids. The results of microscopic examination of a pigmented specimen of skin were strongly suggestive of acanthosis nigricans. On Feb. 13, 1936, we received the report of an operation which this patient had undergone. A supravaginal hysterectomy had been performed, with removal of the appendix. It was noted on exploration that the liver was enormously enlarged, and had a rounded edge and granular surface. The spleen was stated to be six or eight times normal size and the pancreas was enlarged and firm. An unusually large number of enlarged lymph nodes were said to have been present throughout the upper portion of the abdomen and along the great vessels of the back. Biopsy was not made at this time to rule out the possibility of malignancy. The patient's convalescence was uneventful.

CASE 8.—A white man, twenty-five years of age, presented himself at the clinic April 13, 1932, complaining of stomach trouble of five months' duration. At operation, March 1, an inoperable malignant growth was found in the stomach. Following extensive radium treatment there was marked improvement. On June 7, a second exploratory operation was performed and three-fifths of the stomach was removed. There was local lymphatic involvement and extension into the mesocolon. The pathologists reported lymphosarcoma. Convalescence was uneventful and further radium treatments were given. The pigmentation of acanthosis nigricans was then noted. The patient died on November 7, as the result of metastasis.

The following five cases are illustrative of acanthosis nigricans of the juvenile type:

ACANTHOSIS NIGRICANS OF JUVENILE TYPE

CASE 9.—An unmarried woman, aged twenty-four years, came to the clinic on Feb. 17, 1927. She was found to have a small centrally located adenoma of the thyroid gland which we did not think at that time was surgical. General examination was essentially negative. It was also found that her skin was darker than normal, and that this condition had been present approximately since birth. Her

skin had gradually become darker until she was twenty years of age, the condition having then become most marked around the mouth, neck, and abdomen. The skin then became thick and pigmented and verrucous lesions developed. A specimen of skin taken for biopsy confirmed the diagnosis of acanthosis nigricans. In a letter dated March, 1936, the patient stated that the cutaneous lesions and pigmentation had persisted.

CASE 10.—A married woman, aged twenty-three years, came to the clinic Sept. 2, 1929, complaining of stomach trouble. She was found at that time to have exophthalmic goiter and syphilis of the central nervous system. She also had hypertension and pyuria. Examination revealed marked acanthosis nigricans of both axillae, with a slight increase of pigmentation, which was confirmed histologically. There were also numerous pigmented areas on the body, with indurated and thickened skin, which the patient said had been present to some extent for eight and a half years. A specimen removed from the axilla for biopsy showed the typical picture of acanthosis nigricans. The patient had had fairly intensive treatment for syphilis before she came to the clinic, but this had no relation to, or effect on, the changes in the skin. She undoubtedly had a mild polyglandular dyscrasia; she had the male type of pelvis, trunk and extremities, irregular menstrual periods, and a tendency toward nymphomania. It is possible that some suprarenal deficiency played a part in the disease. A letter written in 1934 informed us that the patient had died on Jan. 10, 1932. She had had a stroke thirty days before her death. The local physician said she died of bacteriuria(?).

CASE 11.—A white woman, twenty-two years of age, came to the clinic Dec. 10, 1930, complaining of attacks of abdominal pain which occurred at indefinite intervals and began suddenly following dietary indiscretions. The pain was sharp and was localized in the right side. It was associated with nausea and vomiting and was usually relieved by soda, although on one occasion a hypodermic injection of morphine was necessary. General physical examination gave negative results. A roentgenogram of the gallbladder showed it to be functioning poorly and to be filled with stones. At operation, December 16, the gallbladder and appendix were removed because of subacute cholecystitis and chronic appendicitis. Convalescence was uneventful. The patient was then sent to the Section on Dermatology and Syphilology because of an acneform eruption of the face. Early but definite lesions of acanthosis nigricans were found in the axillae. On subsequent examination, April 14, 1931, axillary lesions were found to be still present.

CASE 12.—A man of Norwegian parentage, aged nineteen years, presented himself at the clinic Feb. 27, 1931, for general examination. He offered no complaints except for persisting acne formation on his face, which had been present for about three years. Physical examination gave essentially negative results except for indicating excessive accentuation of pigment in the groin, axillary and flexural folds of the skin, and acneform lesions on the face and back. A diagnosis of acanthosis nigricans was confirmed by biopsy. Roentgenologic examination revealed a duodenal ulcer with obstruction, and gastric analysis revealed a total acidity of 94, free hydrochloric acid of 82, and retention of 240 c.c. It was decided to defer exploration and have the patient return at monthly intervals for reexamination. He failed to return, however, until Feb. 20, 1935, at which time there was no change in the acanthosis nigricans and his general health was good.

CASE 13.—A married woman, aged twenty-nine years, was first seen at the clinic Nov. 13, 1934, because of pregnancy. Cesarean section was performed May 24, 1935, and a normal male child was delivered. The patient made a good recovery. She returned to the clinic on August 15 because of an infected mosquito bite on her ankle. She was found at that time to have hyperpigmentation in both axillae and

on the neck; she said that this had been present for ten years. A specimen was removed from the right axilla and the diagnosis of acanthosis nigricans was confirmed There was no indication of any malignant condition at that time.

COMMENT

Our experience certainly indicates a definite relationship between the adult type of acanthosis nigricans and some abdominal malignant condition. In 10 of the 218 cases in the literature reviewed by Mukai the primary malignant growth was in the pelvis, in 7 of these cases being in the uterus. In one other case the growth was probably a Krukenberg tumor. Next to the stomach, the generative organs are the most frequent site of the primary malignancy in acanthosis nigricans. Metastatic lesions in the abdomen from cancer of the breast are not uncommon. Cause of death is known in 86 cases. In Mukai's article, which is the most comprehensive review of cases reported in the literature, the stomach was involved primarily in 58 cases (61 per cent) and the generative organs in 11 cases (11.7 per cent). Yet as Moncorps says, "The distinction between benign and malignant forms is not always a sharp one." However, most authors have failed to consider the relative percentage of malignancies according to decades of life.

The cutaneous manifestations in the adult type of acanthosis nigricans, according to some authors, may precede the systemic symptoms of malignancy by five to ten years; personally we would look upon the cases as having a juvenile type of acanthosis nigricans with the development in late life of malignancy; in other cases, cutaneous changes appear after a malignant condition is well established. In the majority of cases, however, the cutaneous changes and symptoms of malignancy develop about the same time. If there is any doubt about the diagnosis a specimen of skin should be taken for biopsy, and when the diagnosis is established, exploratory laparotomy is indicated in the case of adults, especially those in whom the onset is after forty years of age. When acanthosis nigricans develops after an operation for cancer, it usually signifies rapid cachexia and death. Involution of changes in the skin has been reported in only one case, and that was reported by Spietschka. In this case, that of a woman aged nineteen years, after a successful radical operation for probable uterine carcinoma the symptoms and signs of acanthosis nigricans entirely disappeared one and a half years later.

SUMMARY AND CONCLUSIONS

Acanthosis nigricans is probably attributable to a lesion or functional disturbance of the abdominal sympathetic system. When adults are affected, it frequently signifies an associated malignant condition in the abdomen. The probability is that the condition is much more common than published statistics would indicate.

Pigmentation is the result of a deposit of melanin in the basal or dendritic cells of the epidermis. It is symmetrical in distribution, being most marked in the axillae, on the neck, and around the genitalia and other flexural surfaces, including the umbilicus and under the breast. In this respect it resembles Addison's disease, but the verrucous and papillomatous changes permit differentiation both clinically and pathologically.

The prognosis in the juvenile type is good, whereas in the adult type it is grave, increasingly so in the later decades of life. Of the cases of acanthosis nigricans seen at the clinic, 5 of the juvenile type and 8 of the adult type, all the latter were probably associated with abdominal malignancy. Two of the 8 patients with the adult type of acanthosis nigricans are still living, 1, two months following operation elsewhere and the other five months following operation at the clinic. Next to the stomach, the uterus is the most frequent site of malignant disease in cases of the adult type of acanthosis nigricans.

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Item

American Board of Obstetrics and Gynecology

The next written examinations and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology will be held in the various cities in the United States and Canada on Saturday, November 7, 1936, and on Saturday, March 6, 1937.

The next general examination for all candidates (Groups A and B) will be held in Atlantic City, N. J., on June 8 and 9, 1937.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's office not later than sixty days prior to the scheduled date of examination.